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Alimentary Tract

Intestinal metaplasia in Barrett's oesophagus: An essential factor to predict the risk of dysplasia and cancer development

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ABSTRACT

Background: To date, there is still uncertainty on the role of specialized intestinal metaplasia in the carcinogenic process of Barrett's oesophagus (BE); this fact seems of importance for planning adequate surveillance programs.
Aims: To predict the risk of progression towards dysplasia/cancer based on typical morphological features by evaluating the importance of intestinal metaplasia in BE patients.
Methods: 647 cases with a histological diagnosis of BE, referred to the Endoscopy Unit of a tertiary centre between 2000 and 2012 were retrospectively identified, and divided into two groups according to the presence/absence of intestinal metaplasia. For each patient, all histological reports performed during a follow-up of 4–8 years were analyzed.
Results: Overall, 537 cases (83%) with intestinal metaplasia and 110 cases (17%) without intestinal metaplasia were included. During the follow-up period, none of the patients without intestinal metaplasia developed dysplasia/cancer nor progressed to metaplasia, whereas 72 patients with intestinal metaplasia (13.4%) showed histological progression of the disease.
Conclusion: The histological identification of intestinal metaplasia seems to be an essential factor for the progression towards dysplasia and cancer in BE patients.

1. Introduction

The association between Barrett's oesophagus (BE), dysplasia and adenocarcinoma was established several years ago, when patients presenting with adenocarcinoma were often found to have areas of intestinal metaplasia surrounding dysplastic areas, without evidence of neoplastic transformation occurring within fundic and cardiac epithelia [1–3]. Soon, convincing data emerged on the fact that adenocarcinomas developed only in the type of BE containing intestinal metaplasia [4].

Several authors have tried to predict the risk of dysplasia/cancer development based on the presence/absence of intestinal metaplasia, pointing out the need for a clearer definition of BE to plan adequate surveillance programs. For instance, some authors provided evidence that the risk is clearly related to the presence of intestinal metaplasia [5], and others showed that when intestinal metaplasia is absent using an adequate biopsy protocol, the patient has extremely low or no risk of dysplasia and cancer [6]. Other studies stressed the importance of adequate sampling to detect intestinal metaplasia in BE [7,8].

However, other authors reported an increased risk of oesophageal adenocarcinoma even in non-intestinalized BE [9,10] and suggested that surveillance in visible BE should not be based on the presence or absence of intestinal metaplasia. These observations led to the proposal of looking for molecular evidence suggesting that the non-goblet epithelium in BE is biologically intestinalized, since similar DNA abnormalities are present in intestinalized and non-intestinalized BE [11].

Purpose of the present study was to assess the neoplastic risk prediction on the basis of histology at baseline in a large cohort of BE patients, focusing on the importance of intestinal metaplasia.

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2. Patients and methods

2.1. Patients

This was a retrospective study in a tertiary referral centre. The endoscopic database was searched for the term "Barrett's oesophagus" (BE). From 2000 to 2012, 647 cases with a first histological diagnosis of BE were identified. Biopsies from each case were obtained by means of the so called "Seattle protocol" consisting of four-quadrant jumbo biopsies performed every 1 cm from the gastroesophageal junction to the neosquamocolumnar junction and correctly oriented on acetate cellulose filters [12]. All cases were morphologically reanalyzed and divided into two categories according to the type of columnar epithelium: gastric (with cardiac or fundic metaplasia) and intestinal (with intestinal metaplasia, i.e. the presence of goblet cells). Surveillance in all cases was conducted according to international guidelines [13]; the biopsies performed during follow-up (ranging from 4 to 8 years) were also reanalyzed, including report of dysplasia and/or cancer, by two expert pathologists (VV, MS).

2.2. Study protocol

For each patient, the histology slides were stained at the time of diagnosis with hematoxylin–eosin (HE); to confirm the presence/absence of goblet cells an additional stain with PAS-Alcian blue was also performed. Histology slides related to biopsies performed during the follow-up period were stained with HE; in selected cases, when the presence of dysplasia was less obvious on HE, immunohistochemistry for p53 (DO7 antibody, Thermoscientific, USA), Her2 (CB11 monoclonal antibody, Bond Oracle Her2 IHC system, Leica Biosystems, Newcastle, United Kingdom) and p16 (E6H4 antibody, CINtec, Ventana Medical Systems, Roche Diagnostics, USA) was carried out. Her2 overexpression on immunohistochemistry was also confirmed by fluorescence in situ hybridization (FISH, PathVysion HER-2 DNA Probe Kit, Vysis Inc., Downers Grove, IL, USA) in some selected cases. The diagnosis of cancer was made when neoplastic cells penetrated through the basal membrane of crypts in the *lamina propria*.

Since this was a retrospective study, no individual patient identification was involved and no study-driven clinical intervention was performed, therefore, no ethical committee approval was necessary.

3. Results

Of the 647 cases retrieved, 110 featured gastric type BE (17%, cardiac or fundic metaplasia) and 537 intestinal type BE (83%, intestinal metaplasia). The first group was composed of 70 males (age range: 2–86 years) and 40 females (age range: 2–87 years); the latter comprised 418 males (age range: 9–89 years) and 119 females (age range: 13–90 years). During the endoscopic follow-up period (average ranging from 4 to 8 years) no cases with gastric type BE developed dysplasia and/or cancer; moreover, after an average of 4 years' follow-up, no subjects found negative at baseline progressed to intestinal metaplasia. Conversely, 72 cases with intestinal type BE (13.4%) showed histological progression, either towards dysplasia or cancer. In particular, the presence of dysplasia was documented in 40 intestinal type BE cases; it was then classified into low ($n = 22$) and high ($n = 18$) grade dysplasia (Fig. 1). The selected cases in which dysplasia was less obvious on HE stain underwent immunohistochemical analysis for p53, Her2 and p16. Two immunohistochemical patterns were observed in these patients; 52 cases expressed p53 and Her2 and lacked p16, whereas in the remaining cases the lack of p53 and Her2 was associated with the expression of p16 (Fig. 2). Her2 overexpression on immunohistochemistry was also confirmed by FISH in 6 cases.

4. Discussion

In this study we report our experience in 647 BE cases, in which biopsies were obtained through an adequate biopsy sampling protocol; in 17% gastric metaplasia was observed, while 83% showed intestinal metaplasia. Our data confirm that the detection of

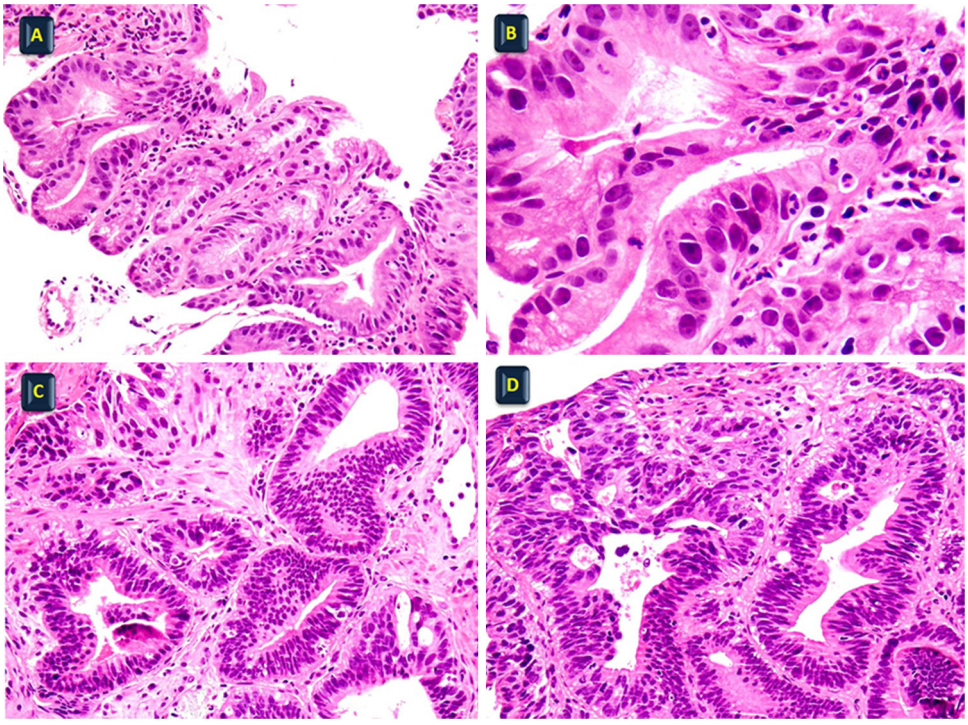

Fig. 1. Barrett's oesophagus histology. Panels A and B: Low-grade dysplasia. Panels C and D: High-grade dysplasia (H&E 40×).