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The importance of a second opinion in the diagnosis of Barrett's esophagus: a "real life" study

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ABSTRACT

Background: Barrett's esophagus is a precancerous lesion, and its identification with the early detection of dysplasia is of paramount importance to prevent adenocarcinoma onset. However, there is still debate on the correct pathological identification of Barrett's esophagus (and of associated dysplasia), and most studies have been conducted in an experimental setting.

Aims: To assess previous uncertain diagnoses of Barrett's (with and without dysplasia) via a second opinion of an expert pathologist in a real life setting.

Patients and methods: Histological sections of 32 suspected Barrett's patients from ten general Pathology units were centralized into one single unit in which an expert pathologist reviewed the slides blindly.

Results: Overall, in 78% of cases there was diagnostic discordance; in particular, in 64% of cases the presence of low grade dysplasia was not confirmed. Of interest, 28% of cases with the original diagnosis were reclassified as non-Barrett's.

Conclusions: The pathological diagnosis of Barrett's esophagus, especially with regard to the presence of dysplasia, is still misinterpreted, particularly in the setting of general pathology units. Thus, a second opinion from an experienced pathologist may help in the interpretation of the results and in starting appropriate follow-up programs.

Key words: Barrett's esophagus. Dysplasia. Endoscopy. Histological concordance.

INTRODUCTION

Barrett's esophagus (BE) is defined as the presence of columnar metaplasia of the distal esophagus (1) and is considered as a complication of chronic gastroesophageal reflux, representing a major risk factor for the development of esophageal adenocarcinoma, the incidence of which has rapidly increased over the past decades (2,3).

The prevalence of BE in patients undergoing endoscopy is 1%, and reaches 3% taking only into account the patients with reflux symptoms (4). According to the Montreal definitions, the term endoscopically suspected esophageal metaplasia (ESEM) describes endoscopic findings consistent with BE that are pending histological evaluation (5). Thus, the aim of the endoscopist is that of documenting the location of the gastro-esophageal junction and the squamo-columnar junction (measured in centimeters from the incisors) and obtaining biopsy samples from any proximal displacement of the latter, that is, suspected BE (6). For this purpose, the more standardized validated method to measure BE is represented by the Prague CM criteria (C = circumferential extent in centimeters; M = maximum extent in centimeters of columnar appearing mucosa in the tubular esophagus) (7). The importance of this classification is highlighted by the fact that the length of BE is associated with a higher prevalence of dysplasia (8). However, adherence to the Prague classification continues to be variable (9,10).

From a pathological point of view, the histological criteria to diagnose BE are variable on a worldwide scale (11). In fact, in Europe and the United States the diagnosis of BE requires the presence (or absence) in esophageal biopsies from endoscopically identified areas of columnar mucosa of intestinal metaplasia, characterized by goblet cells (12-15), whereas the British Society of Gastroenterology requires histological documentation of metaplastic columnar mucosa, but not the presence of goblet cells (16), and in Japan no histological confirmation of endoscopically documented esophageal columnar lined mucosa is required (17).

BE is considered to be a premalignant condition, principally in the presence of intestinal metaplasia, predisposing to adenocarcinoma via a multistep sequence; in this sequence the crucial point is the appearance of dysplasia,

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defined as the histological expression of DNA damage that precedes malignancy. One of the main issues in the diagnosis and grading of dysplasia in BE is the wide inter-observer variability between pathologists, especially when biopsies are assessed by general pathologists (18-20), although this is not much better among expert gastrointestinal pathologists, since there is evidence of only moderate inter-observer agreement in diagnosing early and late dysplastic lesions in BE (21). Therefore, at present, recommendations are based on the agreement by at least two gastrointestinal pathologists after an initial diagnosis of dysplasia in BE is made (22). However, it must be kept in mind that all the above considerations originate from clinical trials, often investigating selected patients from referral centers, and almost no studies on "real life" situations are available.

The purpose of the present study was to assess the routinely diagnostic pathologic agreement with a second expert opinion after an ESEM is identified and an initial difficult/doubtful diagnosis of BE, with or without dysplasia, is made.

MATERIALS AND METHODS

Study protocol

This was a retrospective study organized by the Italian Society of Digestive Endoscopy (*Società Italiana di Endoscopia Digestiva,* SIED), between December 2012 and September 2015. Ten Gastroenterology and Pathology units centralized routinely stained hematoxylin-eosin slides from patients diagnosed with ESEM with an initial uncertain diagnosis of BE, and these were assessed by an expert gastrointestinal pathologist with longstanding interest in BE (VV).

Data analysis

The pathological slides were blinded and coded by the sending pathologist, and then read in blind by another pathologist (VV), who was unaware of the diagnosis formulated in the original Pathology Unit. The diagnosis of BE and grading of dysplasia (if present) was made according to previously described criteria (14,15,23), which included the presence of intestinal metaplasia, characterized by goblet cells.

The concordance between the original diagnosis and the second expert opinion was expressed as a percentage and also analyzed by means of the Cohen's kappa statistic (K) (24). According to Fleiss et al. (25), K is 1 when there is perfect agreement between the classification systems, K is 0 when there is no agreement other than that expected by chance, and K is negative when the agreement is lower than that expected by chance.

Ethical considerations

This was a retrospective study, no individual patient identification was used and no study-driven clinical intervention was performed. Therefore, no ethical approval was necessary.

RESULTS

In the study period, samples from 32 ESEM patients (10 women, 22 men, median age 59 years [95% CI 51-62]) were received. The median number of biopsy samples (obtained according to the Seattle protocol) for each patient was 7.4, and no patient had esophagitis at the time of sampling. Table I shows the description of ESEM, the original (first) pathological diagnosis, and the second expert pathological revision.

Overall, in 25/32 (78%) of cases there was no diagnostic concordance, with a K = -0.021 (agreement lower than that expected by chance). In particular, in 16 cases (64%) the presence of low-grade dysplasia (LGD) was not confirmed by the experienced pathologist, that in these cases reported only the presence of BE without dysplasia, and LGD was confirmed in only 3/19 (16%) cases. Of interest, 7/25 cases (28%) with an original diagnosis of BE were defined as "carditis without morphological features suggesting BE". In one case (#12) the dysplasia was not correctly graded, while in another case (#19) the "second opinion" prevented the use of the term "indefinite for dysplasia". Figures 1 and 2 show representative pathologic cases.

DISCUSSION

This study, carried out in real life conditions (*i.e.,* outside formal research trials), once again highlights the problem of biopsy interpretation in BE, not limited to the identification of dysplasia. In fact, the level of discrepancy we found in our series (78%) suggests that in the daily routine, this issue may be even more worrisome than thought based on the data inferred by research trials (18-21), even though two recent studies on consistent cohorts of patients showed that only 27% of the initial diagnoses of LGD and 51% of those of high-grade dysplasia were confirmed after a second opinion by experienced pathologists (26,27). With regard to the classification of dysplasia, there are several objective reasons that make it sometimes difficult for the pathologist to provide an accurate grading: when erosion, ulcerations, or active inflammation is present, regenerating Barrett's epithelium may feature cytologic aspects resembling dysplasia (28); in addition, biopsies may be poorly oriented or have artifacts, thus limiting an accurate evaluation of dysplasia that may be present. It is common knowledge that for the above considerations a wide variability exists among pathologist in formulating this diagnosis, that is mostly based on the personal experience with this specific area (20,29). This is the reason why a "second look" by an experienced pathologist is usually recommended when dysplasia in BE is found (22).

Of interest, in our opinion, is the fact that almost 30% of ESEM classified as BE by the first pathological assessment were actually not confirmed by the second review. This aspect is not usually mentioned in the literature, and

Table I. CM classification of ESEM, first diagnosis, and second diagnosis by an expert gastrointestinal pathologist in a series of 32 patients

Case	*ESEM (CM classification)*	*First diagnosis*	*"Second opinion" diagnosis*
1	C2M5	LGD in BE	LGD in BE
2	C3M4	LGD in BE	LGD in BE
3	C0M1	LGD in BE	BE without dysplasia
4	C10M10	LGD in BE	BE without dysplasia
5	C2M3	LGD in BE	BE without dysplasia
6	C1M1	LGD in BE	BE without dysplasia
7	C1M1	LGD in BE	BE without dysplasia
8	C3M4	LGD in BE	LGD in BE
9	C4M11	BE without dysplasia	BE without dysplasia
10	C1M3	BE without dysplasia	Carditis
11	C0M1	LGD in BE	BE without dysplasia
12	C9M10	HGD in BE	LGD in BE
13	C3M3	BE without dysplasia	Carditis
14	C2M2	BE without dysplasia	Carditis
15	C1M2	BE without dysplasia	Carditis
16	C0M2	LGD in BE	BE without dysplasia
17	C4M5	LGD in BE	BE without dysplasia
18	C7M9	LGD in BE	BE without dysplasia
19	C1M4	Indefinite for dysplasia in BE	BE without dysplasia
20	C3M2	BE without dysplasia	Carditis
21	C0M0	LGD in BE	BE without dysplasia
22	C0M4	LGD in BE	BE without dysplasia
23	C3M5	LGD in BE	BE without dysplasia
24	C0M1	LGD in BE	BE without dysplasia
25	C0M1	LGD in BE	BE without dysplasia
26	C2M1	LGD in BE	BE without dysplasia
27	C3M2	BE without dysplasia	BE without dysplasia
28	C2M3	BE without dysplasia	BE without dysplasia
29	C2M3	BE without dysplasia	Carditis
30	C2M3	BE without dysplasia	BE without dysplasia
31	C2M3	BE without dysplasia	Carditis
32	C0M2	LGD in BE	BE without dysplasia

studies have mainly focused on recognition of intestinal metaplasia in BE (30) or dysplasia in BE (20,31,32). A recent study evaluating inter-pathologist variability in the interpretation of columnar-lined esophagus showed a poor/fair concordance rate (K = 0.17, CI 0.16-0.19) in identifying possible BE without intestinal metaplasia (33). Once again, the agreement was greater between gastrointestinal pathologists than in other general pathologists.

Without doubt, there is a strong need for a better approach to BE patients, especially from a pathologic point of view. In fact, since it is well known that Barrett's epithelium may progress to adenocarcinoma over a period of time (34,35), it is of paramount importance to detect the early phases of neoplastic transformation, that is, LGD. Since patients with BE usually enter a surveillance program (36), and the finding of dysplasia prompts repeated endoscopic and pathologic controls (37), thus raising the health costs (38), efforts should be made not to overemphasize the diagnosis of dysplasia in this setting. On the other hand, further efforts should be made to obtain diag-

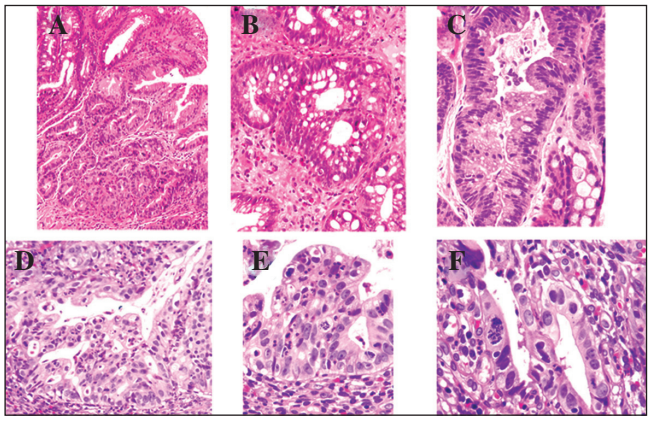

Fig. 1. Representative cases of Barrett's esophagus without dysplasia, but with only hyperplastic reactions (H&E; original magnification A, x 10; B, x 20; C, x 40; D-F, same case, x 20, x 40 and x 100, respectively).

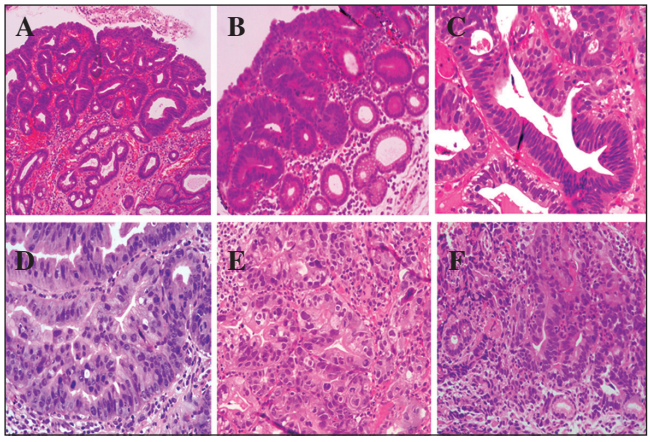

Fig. 2. Representative cases of Barrett's esophagus with dysplasia. A-C. Low grade dysplasia (H&E; original magnification A, x 10; B, x 20; C, x 40). D-F. High grade dysplasia (H&E; original magnification D and E, x 40; F, x 20).

noses as precise as possible, and the "second look" by an experienced pathologist might thus help in downstaging (or confirming) dysplasia grade, in order to improve the effectiveness of surveillance programs and to reduce costs. However, the road leading to this goal still appears quite long, since even the newer endoscopic image processing have so far not proven to be superior to white light imaging in screening programs for BE (39,40), although other more sophisticated techniques might offer better perspectives (41,42). At the same time, the histological descriptions are strictly dependent on the experience of the pathologists. In particular, it is important to keep in mind the characteristics of the architecture of the crypts (back to back in LGD, fused in high-grade dysplasia), the cytological characteristics (hyperchromatic nuclei in LGD, vesicular in high-grade dysplasia), and nucleoli (inconspicuous in LGD prominent in high-grade dysplasia).

Of course, this study has limitations, being the main one due to the relatively small sample size. However, this study was meant as a way to test the possible daily problems in diagnosing cases of BE in real life conditions, outside of the strict limits imposed by formal research trials in which there is a more specific focus on the topic.

In conclusion, the pathological assessment of BE and dysplasia in BE is still quite difficult, and especially in the daily routine subjected to sensitivity bias. Once again, the importance of a second opinion by an experienced pathologist (whenever possible or available) is stressed, especially when dysplasia is found. Educational programs should be implemented to improve the diagnostic accuracy in this field.

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