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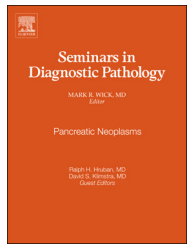

Predictive value of immunohistochemistry in pre-malignant lesions of the gastrointestinal tract

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ABSTRACT

Immunohistochemistry can be an important adjunct to histopathology for the diagnosis of pre-malignant lesions of the gastrointestinal tract and in patient risk stratification. The purpose of this review is to provide information and guidance on the usefulness of immunohistochemical markers that facilitate the diagnosis of dysplasia and help to predict risk for the development of carcinoma in pre-malignant lesions of the gastrointestinal tract. Particular emphasis is given to the role of immunohistochemistry in the assessment of epithelial dysplasia in the setting of Barrett's esophagus and inflammatory bowel disease; supplementary immunohistochemistry for subtyping adenomas of the stomach and ampulla and serrated polyps of the colon and rectum; and ancillary markers of squamous neoplasia of the anal canal.

Introduction

Gastrointestinal (GI) tract carcinomas often follow the dysplasia–carcinoma sequence with stepwise progression from pre-malignant lesions including flat dysplasia and adenoma to *in-situ* and invasive carcinoma. During the progression to malignancy, stepwise accumulation of genetic alterations occurs; these alterations often parallel the severity of dysplasia. In current clinical practice, screening of patients at risk by surveillance endoscopy and biopsy is the primary strategy for preventing death from GI tract carcinoma. Pathologists play a critical role in patient risk stratification by grading surveillance biopsies for dysplasia and performing ancillary tests for additional risk assessment. The purpose of this review is to provide up-to-date information and guidance on the usefulness of immunohistochemical (IHC) markers that facilitate the diagnosis of dysplasia and help to predict risk for the development of carcinoma in pre-malignant lesions of the upper and lower GI tract.

Upper gastrointestinal tract

Barrett's esophagus

Barrett's esophagus (BE) is a preneoplastic condition that is the precursor to esophageal adenocarcinoma. The incidence of adenocarcinoma associated with BE without dysplasia is approximately 0.5% per year.[1] In contrast, the incidence of esophageal adenocarcinoma among patients with high-grade dysplasia (HGD) ranges from 5.6% per year to 6.6% per year.[2] Thus, the diagnosis of BE and BE-related dysplasia is critical in patient risk stratification and clinical management.

BE-related dysplasia diagnosis on surveillance biopsies has considerable issues with intra- and inter-observer reproducibility. Surrogate IHC markers have been explored in an attempt to improve the diagnosis and grading of BE-related dysplasia. IHC with antibodies against TP53 is the most studied and is the most widely used marker. Mutated forms of TP53 accumulate in the cell nucleus and therefore they can

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be detected by IHC. In general, TP53 immunoreactivity tends to increase with the severity of BE-related dysplasia. *TP53* mutation has been reported in 1–5% cases of BE without dysplasia, up to 65% of BE with LGD, up to 75% with HGD, and 50–90% of adenocarcinoma arising in BE-related dysplasia.[3] However, TP53 immunoreactivity can be detected in up to 10% cases of BE without dysplasia[4] and not in all cases of BE with HGD.[5] These findings limit the utility of TP53 IHC in assisting the diagnosis of dysplasia. In daily pathology practice, TP53 IHC is mainly used to confirm the histologic interpretation of HGD, especially when the worrisome focus of dysplastic epithelium is obscured by a prominent inflammatory component. TP53 nuclear labeling can be seen in the bottom portion of the BE glands without dysplasia and should not be misinterpreted as positive/true TP53 immunoreactivity (Fig. 1). Positive TP53 immunostaining is the strong/intense nuclear staining that can be appreciated even at low magnification (objective lens × 4 for example). The nuclear labeling should be restricted to the dysplastic cells/glands and extend onto the surface in BE with HGD (Fig. 1). In BE with LGD, strong/intense TP53 nuclear labeling is seen in the deep portions of the dysplastic cells/glands with focal extension onto the surface (Fig. 1).

Similar to TP53, Ki67 has also been extensively studied in facilitating the diagnosis of BE-related dysplasia. Ki67 is a nuclear protein expressed in only proliferating cells and the MIB-1 monoclonal antibody has been widely used to detect nuclear expression of Ki67 as an index of proliferation. Overexpression of Ki67 is seen in BE; the distribution of Ki67 labeling has been shown to correlate with the degree of

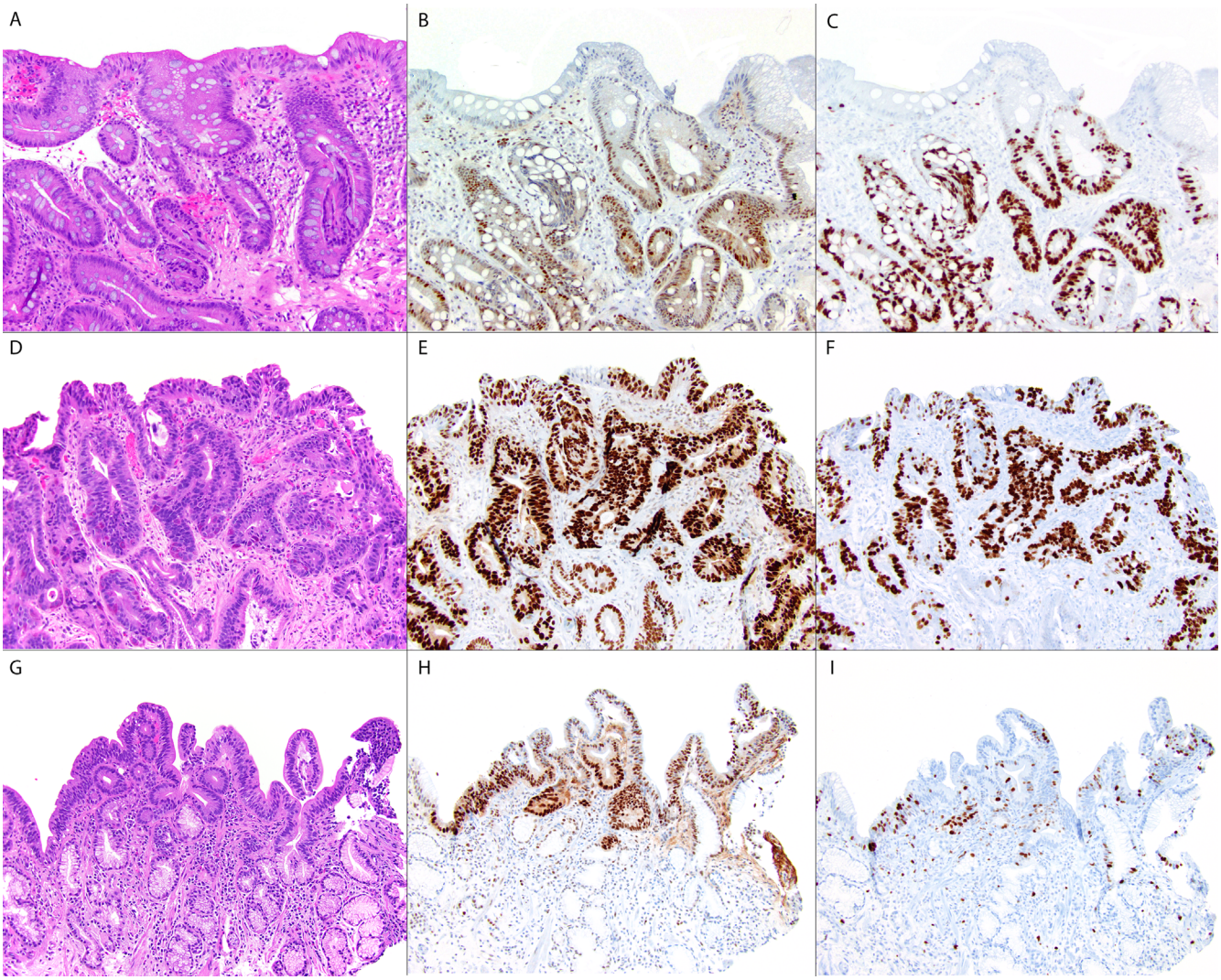

Fig. 1 – (A) H&E of Barrett's mucosa without dysplasia showing goblet cells, i.e., intestinal metaplasia. (B) TP53 immunohistochemistry demonstrating weak-to-moderate staining limited to the bottom of glands. (C) Ki-67 immunohistochemistry demonstrating staining at the bottom of the glands. (D) H&E of Barrett's mucosa with high-grade dysplasia. TP53 (E) and Ki-67 (F) immunohistochemistry demonstrating strong/intense nuclear staining in both deep portions and the surface of the dysplastic glands. (G) H&E of Barrett's mucosa with low-grade dysplasia. (H) TP53 immunohistochemistry demonstrating strong nuclear staining predominantly restricted to the upper portions of the dysplastic glands with extension to the surface. (I) Ki-67 immunohistochemistry showing strong nuclear staining in upper portion of the dysplastic glands.