Recognition of the null staining pattern increases the utility of p53 IHC in Barrett's esophagus

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Abstract

Background: Mutation and/or deletion of p53, a cell cycle regulatory gene, is a promising biomarker for predicting the risk of neoplastic progression in Barrett's esophagus (BE). Although overexpression of p53 by immunohistochemistry (IHC) is a useful surrogate for point mutations, complete absence of p53 protein by IHC in neoplastic cells (null pattern) has recently been shown to be highly correlated with truncation and deletion mutations. This study was designed to evaluate p53 expression patterns in BE with and without dysplasia.

Design: 2,817 biopsies with a diagnosis of BE with or without dysplasia that also had a p53 IHC stain performed between Jan. 1, 2010, and Nov. 12, 2012, were identified in the files of Miraca Life Sciences. This included 1,339 with high-grade dysplasia (HGD), 2,747 with low-grade dysplasia (LGD), 2,142 indefinite for dysplasia (IND), and 2,190 negative for dysplasia (ND). IHC stains were classified as: wild type (WT, 1-15% nuclear staining), low grade (LGD), 214 indefinite for dysplasia (IND) and 2190 negative for dysplasia (ND). BE with HGD compared to LGD, IND, and ND (32/133, 24.1% vs. 38/309, 12.3%, p=0.0019). 133/139 (95.7%) of HGD had abnormal p53 IHC.

Results: Abnormal p53 IHC expression patterns were detected in 442/2,817 (15.7%) biopsies, including 372/442 (84.2%) with PMP, 57/442 (12.9%) with NMP, and 13/442 (2.9%) with both patterns in the same biopsy. 70/442 (15.4%) of the p53 abnormalities were NMP, representing an 18.8% (70/372) increase in the total number of abnormalities detected. The frequency of p53 mutation patterns correlated with increasing grades of dysplasia (Figure 2). While both PMP and NMP were identified in cases with and (rarely) without dysplasia, NMP was disproportionately found in biopsies with HGD compared to LGD, IND, and ND (32/133, 24.1% vs. 38/309, 12.3%, p=0.0019). 133/139 (95.7%) of HGD had abnormal p53 IHC.

Methods: We hypothesized that recognition of the p53 null staining pattern would increase the sensitivity of IHC for the detection of p53 alterations.

The files of Miraca Life Sciences were searched and 2,817 biopsies were identified with a diagnosis of BE, with or without dysplasia, that also had a p53 stain performed between Jan. 1, 2010 and Nov. 12, 2012. The cases included 1,339 with high-grade dysplasia (HGD), 2,747 with low-grade dysplasia (LGD), 2,142 with indefinite for dysplasia (IND), and 2,190 with negative for dysplasia (ND). The vast majority of high-grade dysplasia (95.7%) had a detectable p53 IHC abnormality.

Conclusions: Recognition of the p53 null mutation pattern increases the sensitivity of IHC for detection of p53 abnormalities by 18.8%.

Prior studies that considered null mutation patterns as "wild type" have underestimated the frequency of p53 mutations and, therefore, the possible utility of p53 as a diagnostic aid and predictive biomarker.

References

1 Red Bl et al. Predictions of progression in Barrett's esophagus II: Baseline 17p (p53) loss of heterozygosity identifies a patient subset at increased risk of neoplastic progression. Am J Gastroenterol 2009;104:2673
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Figure 1a: p53 wild-type pattern. There is positivity in about 80% of cells, 2+ positivity in about 3% of cells and 3+ positivity in about 1% of cells.

Figure 1b: p53 point mutation pattern. Crypt epithelium has 2+ positivity in about 20% of cells and 3+ positivity in about 80% of cells. Nuclear positivity extends focally onto the surface.

Figure 1c: p53 null mutation pattern. A single crypt in the center of the field has wild type positivity. Remaining crypts have no nuclear positivity.

Figure 2: Graphic representation of p53 in Barrett's esophagus with and without dysplasia.

Study Highlights

1. There are two distinct abnormal p53 IHC expression patterns in BE, including p53 IHC and dysplasia: the point mutation pattern and the null mutation pattern.
2. The p53 null mutation pattern comprises 15.4% of all detectable p53 IHC abnormalities.
3. The p53 null mutation pattern makes up a greater proportion of detectable p53 abnormalities in high-grade dysplasia (compared to low-grade dysplasia, indefinite for dysplasia and negative for dysplasia).
4. The vast majority of high-grade dysplasia (95.7%) have a detectable p53 IHC abnormality.

References: