Title: **Significant Discordance Between Endoscopy and Biopsy Histology in Assessing Inflammation in Active Crohn's Disease**

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Background: A key feature of mucosal inflammation in Crohn's disease (CD) is its patchiness or focality at both macroscopic and microscopic levels. Discrepancy between endoscopic and histologic assessments for mucosal inflammation in CD, even for the presence of ulceration, is sometimes felt questionable to clinicians and attributed to biopsy sampling error or variation. However, a systematic study on site-specific endoscopic-microscopic correlation is lacking.

Methods: We designed a peri-ulcer multibiopsy protocol to investigate the histologic heterogeneity of inflammation in mucosa surrounding ulcers and to compare with similarly sited ulcer-free mucosa. 33 patients with active Crohn's ileitis (20M/13F, 20 to 72 YO) were enrolled. In 21 patients with discrete ulcer(s) in the terminal ileum, 3 colonoscopic biopsies were taken respectively from the ulcer edge, 7-mm away, and 14-mm from the ulcer edge. The same biopsy protocol was performed in 12 patients without ulcer as a control, but from randomly chosen areas of endoscopically normal-appearing terminal ileal mucosa. Upon histopathologic evaluation, the mucosal inflammation was semiquantitated using three histologic indices: Global Histology Activity Score (GHAS), Robarts Histopathology Index (RHI), and Picasso Histological Remission Index (PHRI).

Results: Of all biopsies from ulcer edges, only 38% (8/21) showed histologic features of ulcer or erosion. Of biopsies from 7mm distant to ulcer, 33% (7/21) showed evidence of active (neutrophilic) inflammation (RHI>3) and 24% (5/21) showed chronic (lymphoplasmacytic) inflammation. Of the biopsies 14mm away from ulcer, 19% (4/21) showed active inflammation and 10% (2/21) showed chronic inflammation. In the no-ulcer controls, none of the biopsies showed features of ulcer or erosion; however, the endoscopically unremarkable mucosa showed active inflammation in 8% and chronic inflammation in 3% on histology.

Conclusions: A strikingly significant discordance exists between endoscopic and histologic assessments for mucosal inflammation in ileal CD. Our findings confirm poor endoscopic-histologic correlation in assessing mucosal inflammation and disease activity in CD, and also raise concern about the appropriateness of current biopsy protocol and histologic scoring for assessing histologic remission and drug effects in clinical trials in patients with CD. Future work is needed to determine a more representative and reproducible biopsy protocol and CD-specific histologic index for CD.