

Expression of Aldehyde Dehydrogenase in Dysplastic Lesions Arising from Inflammatory Bowel Disease

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BACKGROUND

The cancer stem cell (CSC) hypothesis proposes a relatively small population of neoplastic cells have the unique ability to initiate and sustain tumoral growth. Detection of cancer stem cells has been performed with a variety of markers, most notably aldehyde dehydrogenase (ALDH1), responsible for catalyzing the irreversible oxidation of aromatic aldehydes to their corresponding carboxylic acids. Prior work using xenograft models has shown ALDH1⁺ cells from both colorectal adenocarcinoma (CRC) and inflammatory bowel disease (IBD) are capable of promoting tumorigenesis in mice. We hope to expand on previous work through the examination of ALDH1 expression in dysplastic lesions from surgical resections for IBD, thereby illustrating the importance of CSCs in the development of neoplasia arising from an inflammatory background. The distinction between inflammatory change and dysplasia can be difficult, and has significant patient management implications. Increasing levels of ALDH1 may help identify dysplasia, and confirm the role of stem cells in cancer progression.

DESIGN

Fifty-four surgical resections of IBD were studied. All diagnoses were confirmed by at least two experienced pathologists. The diagnostic categories were as follows: 13 high-grade dysplasia / adenocarcinoma, 19 low-grade dysplasia, and 22 inflammatory atypia / negative for dysplasia. Immunohistochemical staining for ALDH1 was evaluated in the cytoplasm of epithelial and stromal cells both on intensity (0-3+), and percentage of cells staining. Criteria for positive staining was modeled after previous work, requiring at least 1+ staining in >20% of cells to be considered positive.

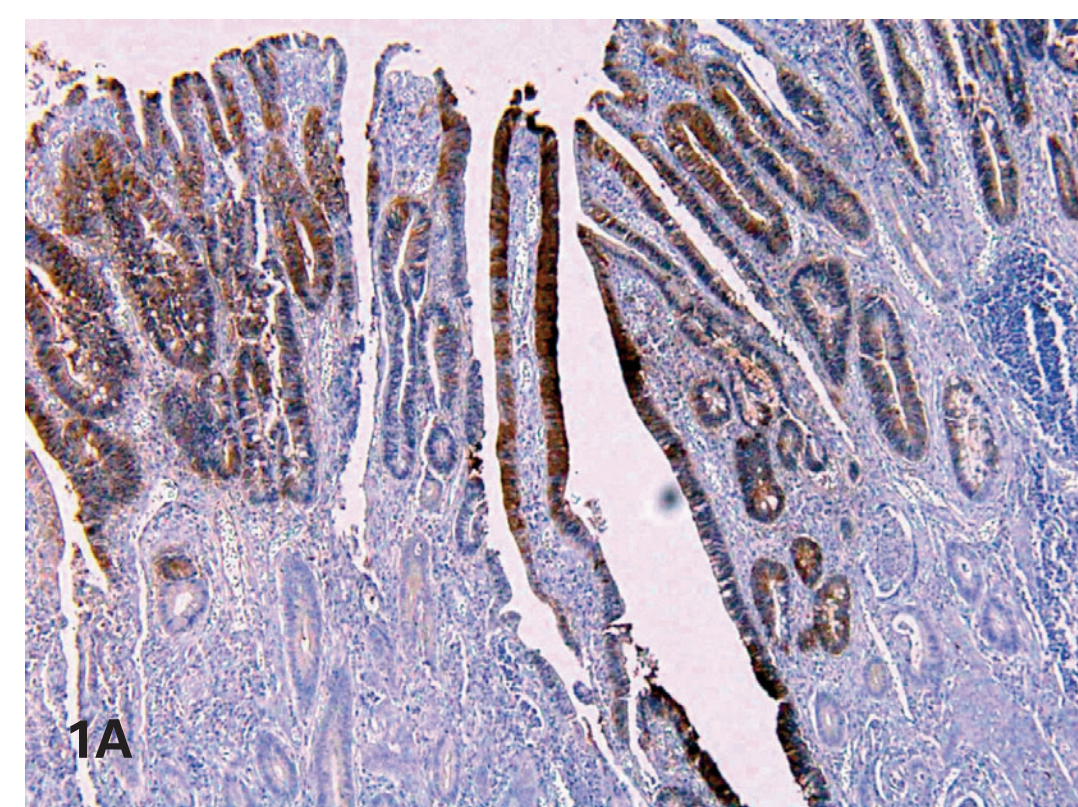


Figure 1A: ALDH1 expression in dysplasia. Diffuse 3+ staining is present throughout the dysplastic glands.

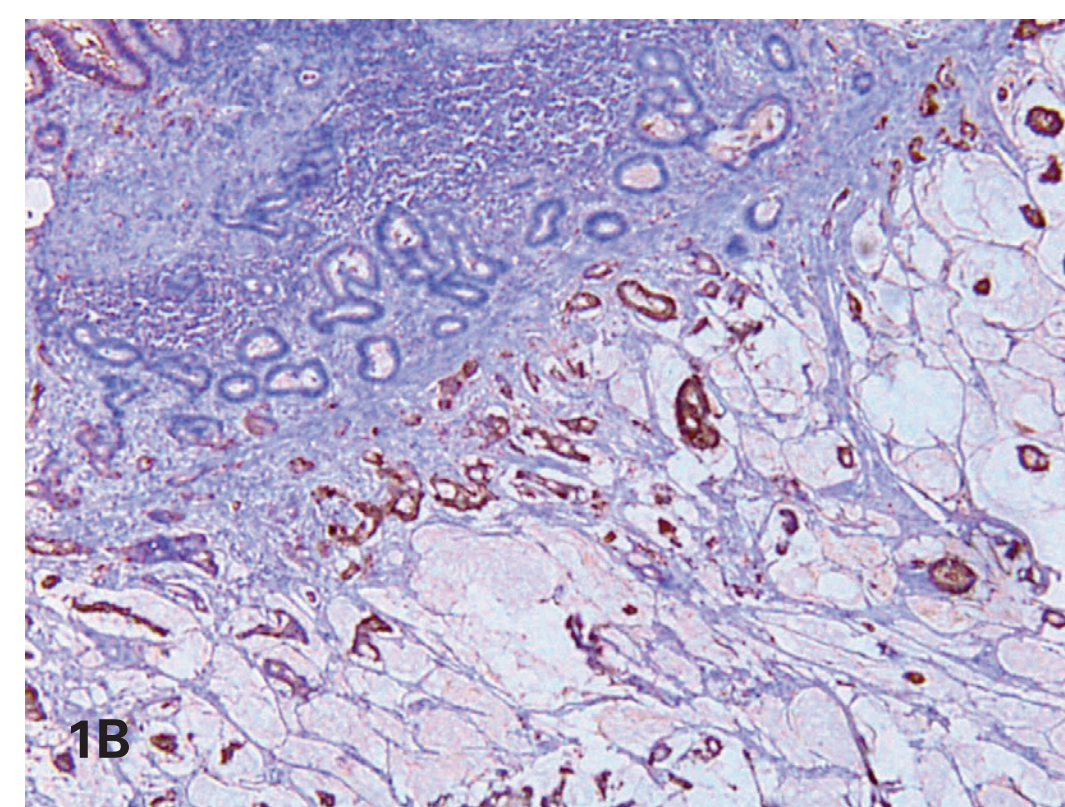


Figure 1B: ALDH1 expression in adenocarcinoma. The invasive component of this colitis-associated adenocarcinoma shows diffuse 3+ staining.

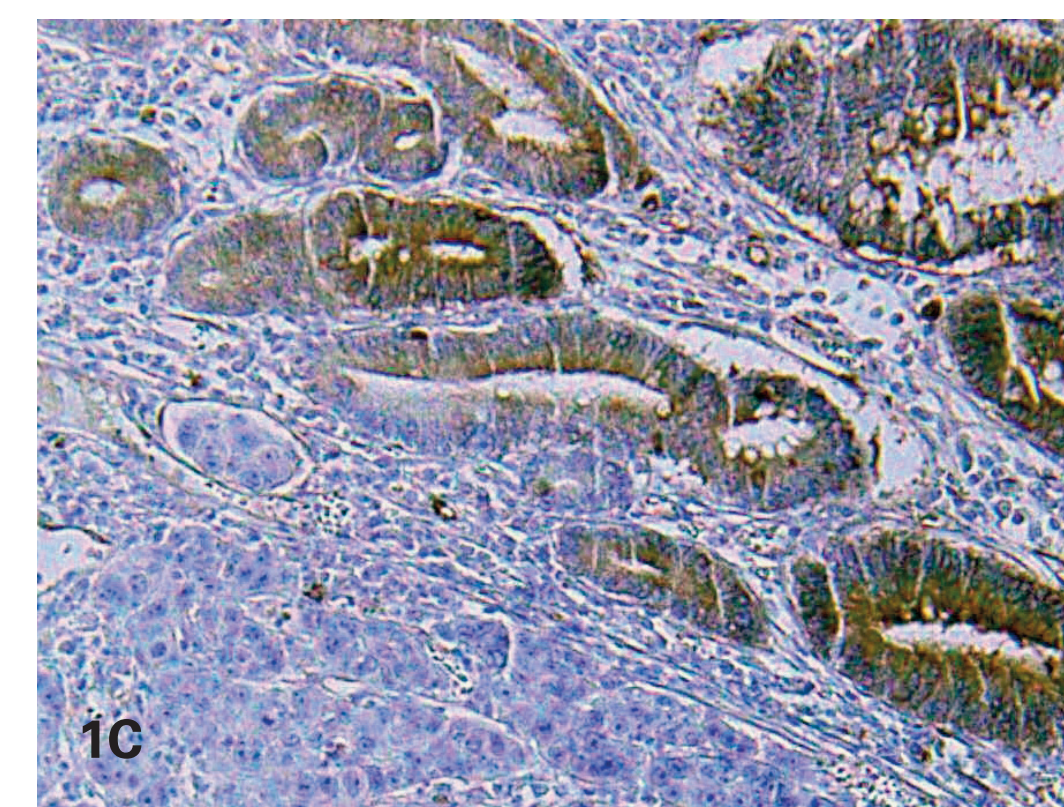


Figure 1C: ALDH1 expression in poorly-differentiated adenocarcinoma. There is a complete lack of staining in the carcinoma, while the overlying dysplastic mucosa shows diffuse 3+ staining.

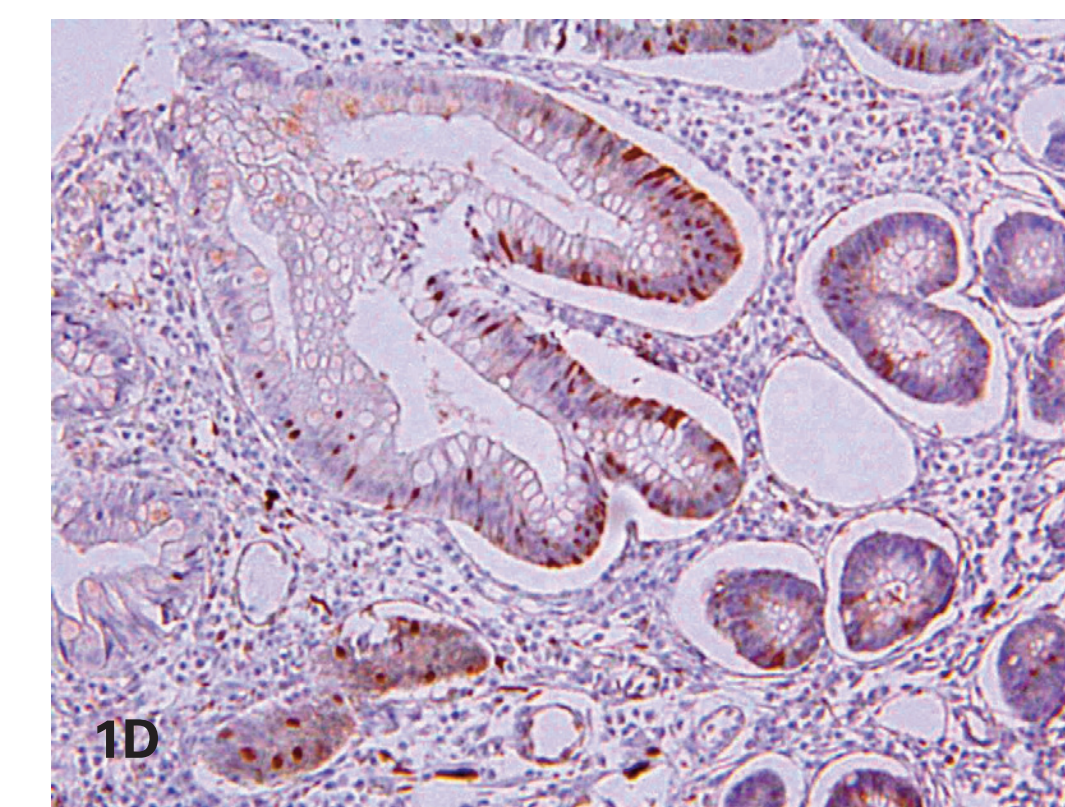


Figure 1D: ALDH1 expression in a case lacking dysplasia. This gland shows architectural changes of IBD, however is negative for dysplasia. ALDH1 staining shows 2+ expression in the inferior portion of the gland.

RESULTS

Patient demographics / follow-up

The study group had the following characteristics: 61% male & 39% female, average age 50 years (range 25-82 years). Total colectomy was performed in 83% of cases. Among patients initially undergoing partial colectomy, 50% went on to have a completion colectomy, while the remaining 50% had surveillance biopsies showing features of inflammatory disease without dysplastic change.

ALDH1 expression

Positive staining was seen in 92% of cases with high-grade dysplasia / adenocarcinoma (12/13), and 95% (18/19) of cases with low-grade dysplasia. Invasive carcinomas showed patchy expression in 33% of cases, while dysplastic mucosa exhibited homogeneous expression extending from the crypt base to superficial mucosa (**Figure 1A**). Although patchy, staining of invasive adenocarcinoma was generally strongest in the advancing front (**Figure 1B**). A notable exception was a poorly differentiated adenocarcinoma which failed to express ALDH1 (**Figure 1C**). Benign mucosa showed patchy focal positivity mainly in the crypt base. Cases with inflammatory atypia (negative for dysplasia) showed positive staining in 45%

(10/22) of cases (**Figure 1D**). Expression of ALDH1 in cases of inflammatory atypia was concentrated in the crypt base in 20% (2/10) of cases, and scattered throughout the crypt in 80% (8/10) of cases. The sensitivity and specificity of ALDH1 for dysplasia was 95% and 55%, respectively.

DISCUSSION

The rationale for our study was based upon the observation that ALDH1 was both a sensitive and specific marker for stem cells. Seventeen isoforms of aldehyde dehydrogenase have been previously described from a wide distribution of differentiated tissue, and with broad cellular distributions. Highest levels are found in the liver, where ALDH1 functions principally in the biosynthesis of retinoic acid. Although retinoids are capable of inducing terminal differentiation in late hematopoietic cells, immature cell populations exhibit enhanced self-renewal in response to increased ALDH1 levels. An important step in the utilization of ALDH1 as a surrogate marker of stem cells was to correlate its expression with more accepted markers of stem cells. ALDH1⁺ cells commonly co-express markers associated with a stem cell phenotype including CD24, CD200, and Oct3/4. Given these properties, it is not surprising increased ALDH1 expression

has been previously correlated with a poor prognosis in a variety of epithelial malignancies.

The mechanism underlying colitis-associated adenocarcinoma has been hypothesized to involve the generation of free radicals and prooxidant molecules contributing to oncogenesis through promotion of genomic instability. The pathways targeted appear to mirror those involved in sporadic CRC, and include allelic loss of tumor suppressor genes and microsatellite instability. While not directly causative in these processes, ALDH1 expression may provide a common link between IBD and neoplasia, and ALDH1⁺ cells from areas of inflammation have the ability to progress to CRC in xenograft studies of NOD-SCID mice.

CONCLUSION

Our study demonstrates ALDH1 is significantly expressed in dysplastic lesions arising from IBD. ALDH1-expression in cancer stem cells suggests an important causative role in the progression to cancer in IBD. Although we found high sensitivity for dysplasia, the specificity was poor. In addition to neoplasia, ALDH1-expressing stem cells proliferate in response to chronic inflammation, accounting for the cases of inflammatory atypia with positive ALDH1 expression.