Sporadic Adenomas and DALMs in IBD

Robert D Odze, M.D., FRCP(c)
Chief, Gastrointestinal Pathology Service
Associate Professor of Pathology
Brigham and Women's Hospital
Harvard Medical School
Boston, MA
Telephone: (617) 732-7549
Fax: (617) 278-6950
E-mail: Rodze@partners.org
Historical Perspective and Classification of DALM’s

There are two general patterns of growth of dysplasia in IBD, commonly referred to as flat (endoscopically undetectable) or elevated (endoscopically detectable)\(^1\)-\(^3\). Elevated lesions are often referred to by the acronym DALM (dysplasia associated lesion of mass)\(^4\). However, as discussed below, there is inconsistency in the published literature with regard to the criteria used to designate a particular dysplastic lesion as a DALM\(^3,5\)-\(^7\). Furthermore, although it is presumed that most, if not all, elevated dysplastic lesion begin as flat endoscopically undetectable areas of dysplasia, this have never been investigated thoroughly. In fact, rarely invasive cancers in IBD may appear as endoscopically undetectable lesions.

In 1959, Dawson et al., in a retrospective study of 17 carcinoma specimens in patients with ulcerative colitis (UC), were the first to described “polypoid lesions” that were histologically indistinguishable from adenomas in 9 of their study patients\(^8\). Subsequently, the results of several studies, all retrospective, defined various types of elevated, grossly visible, dysplastic lesions, some adenoma-like, complicating UC\(^4,5,7,10\). However, it was not until 1981 that the term “DALM” was coined by Blackstone et al\(^4\). In their study, 12 of 112 patients with long-standing UC were found to have a DALM, and of these, 7 (58%) had carcinoma. Given the strong association with cancer, the presence of a DALM constituted a strong indication for colectomy, which has become the standard of therapy for this type of lesion. Since the Blackstone et al. publication, several other studies have confirmed the high association of DALM’s with cancer, a finding related primarily to the fact that biopsies of non-adenoma-like DALM’s often represent the surface of an invasive adenocarcinoma and is one of the major reasons for the high association of DALM’s with cancer in previously reported retrospective studies\(^4,7,10,13\). However, these studies are quite diverse with regard to the definitions used
(including the criteria for dysplasia), the gross features of the DLM’s, the nature of the pathological material (biopsies versus resections), and the clinical and endoscopic features of the lesions. Nevertheless, it is now apparent that DLM’s are a heterogenous population of tumors in which the cancer risk is not equal among these various subtypes.

Recent studies suggest that DLM’s may be broadly separated into those that endoscopically appear similar to non-IBD related sporadic adenomas, herein referred to as adenoma-like, and those that do not resemble adenomas, which are referred to as non-adenoma-like[14-15]. As a common rule of thumb, lesions may be considered adenoma-like if they are amenable to endoscopic resection, and non-adenoma-like if they are not. Based on the widely accepted premise that carcinogenesis in IBD occurs exclusively in areas of mucosa involved with the inflammatory process, it is assumed, and accepted by most investigators, that dysplastic lesions that occur proximal to, or in between, areas of involved colon may justifiably be considered sporadic in origin and, thus, unrelated to the underlying IBD[12]. This classification system is useful both pathologically and clinically, since it helps separate DLM’s into two groups of lesions each with a different natural history, risk of malignancy and treatment[14-17]. For instance, adenoma-like DLM’s possess a low risk of malignancy and may be treated conservatively by polypectomy and continued surveillance, whereas non-adenoma-like DLM’s have a high risk of concurrent malignancy and, as a result, often require colectomy as the definitive form of treatment[4,10,11,14,15]. Unfortunately, there is little data on the incidence of cancer as it relates to the different growth subtypes of non-adenoma-like DLM’s and is an area in need of further research.

There are conflicting data regarding the percentage of elevated dysplastic lesions that are adenoma-like versus non-adenoma like in UC[2,5,7,9-11]. Furthermore, the data in these studies is
difficult to interpret because, in most instances, lesions are simply referred to as “polypoid” without further description. For instance, in one prospective study by Blackstone and one retrospective study by Butt, the prevalence rate of “polypoid” dysplasia in their UC patient cohorts was only 42% and 28% respectively, of the percentage of elevated macroscopically detectable dysplastic lesions. Nevertheless, one recent retrospective endoscopic study by Rutter et al, evaluated 56 patients with UC who developed dysplasia (either flat or elevated) in the course of a 14-year surveillance program conducted at St. Mark’s Hospital in London. Of the 525 patients enrolled in the study, 110 neoplastic areas were detected in 56 patients, of which 77% were visible macroscopically at colonoscopy. More specifically, 74 of the visible lesions (87%) were polypoid (adenoma-like), 4 were described as having an irregular outline, and one was described as a plaque. After excluding 25 lesions that the authors believed represented sporadic adenomas, and 6 biopsy confirmed cancers, 70% of the total number of dysplastic lesions were considered endoscopically visible and 30% were invisible. Thus, the results of this study suggested that most dysplastic lesions in UC are, in fact, endoscopically visible (and, thus considered DALM’s) and that the majority of visible lesions are well circumscribed “adenoma-like” polyps.

Pathology of DALMS

Grossly, adenoma-like DALM’s represent well-circumscribed, smooth or papillary, non-necrotic, sessile, or pedunculated, polyps that, similar to sporadic adenomas, are usually readily accessible to removal by routine endoscopic methods (Table 1). Non-adenoma-like lesions include velvety patches, plaques, irregular bumps and nodules, wart-like thickenings, stricturing
lesions, and broad-based masses\textsuperscript{2,4,9-11}. Non-adenoma-like DALM’s are not usually amenable to removal by colonoscopy.

Non-adenoma like and adenoma-like DALM’s are differentiated on the basis of their gross (endoscopic) features, since histologically, and particularly upon biopsy analysis, both types of lesions may appear identical\textsuperscript{12}. Both types of DALM’s are typically composed of a tubular, tubulovillous, or villous proliferation of “adenomatous” epithelium containing dysplastic columnar cells. Dysplastic columnar cells show pencil shaped, basally located nuclei, pseudostratification and stratification, clumped chromatin, multiple small nucleoli, mucin depletion, increased mitosis (both typical and atypical), nuclear hyperchromaticity and loss of cell polarity\textsuperscript{12,18,19}. A variable degree of acute and chronic inflammation or ulceration may be present as well. Biopsies from non-adenoma like DALM’S may only show fragments of dysplastic epithelium, which as mentioned above, in the majority of instances, simply represents the surface of an underlying carcinoma. In this circumstance, biopsies from deeper portions of the lesion may reveal the characteristic features of invasive adenocarcinoma. Therefore, it is highly recommended that pathologists evaluate both the microscopic and endoscopic features of the lesion prior to establishing a final diagnosis\textsuperscript{17}.

**Differential Diagnosis of Adenoma-Like DALM’s**

The microscopic features of adenoma-like DALM’s are similar to those of sporadic adenomas unrelated to IBD\textsuperscript{12}. There have been several retrospective case-control studies designed specifically to evaluate features that may help differentiate UC-related adenoma-like DALM’s from sporadic adenomas by microscopic, immunohistochemical or molecular methods\textsuperscript{12,18-27}. In one retrospective case-control study by Torres et al, 89 adenoma–like
DALM’s from 59 UC patients were evaluated morphologically. These author’s utilized rigid endoscopic criteria in order to select a homogenous population of DALM’s that resembled sporadic adenomas. The purpose of this study was to determine clinical and pathologic features that may used to separate IBD-related adenoma-like DALM’s from non-IBD related sporadic adenomas. Lesions were characterized as “sporadic adenomas” if they were located proximal to known areas of colitis, and these were compared to adenoma-like DALM’s that occurred within areas of established colitis. Patients with UC related adenoma-like DALM’s had a statistically significant longer duration of disease (greater than 10 years), a higher proportion of polyps with tubulovillous, or villous, architecture, a mixture of normal and dysplastic epithelium at the surface of the polyps, and a higher degree mononuclear inflammation in the lamina propria compared to non-UC related sporadic adenomas. The median age of UC-related lesions was 48 years compared to 63.5 years for patients with sporadic adenomas. UC-related adenoma-like DALM’s also showed a non-statistically significant increase in the degree of neutrophilic inflammation in the lamina propria. The presence of stalk dysplasia has been suggested, anecdotally, to represent a feature indicative of an IBD-related polypoid dysplastic lesion rather than a sporadic adenoma. However, in the study by Torres et al, both UC-related adenoma-like DALM’s and sporadic adenomas had a similar prevalence rate of stalk dysplasia. In addition, patients with UC-related adenoma-like DALM’s may show dysplasia in flat mucosa adjacent to, or distant, from the dysplastic polyp, which is rare in UC patients with sporadic adenomas. Eight patients in that study had Crohn’s colitis, but the distinction between UC and Crohn’s related lesions was not possible morphologically.

In another retrospective cohort study by Suzuki et al, 27 UC patients with “macroscopic neoplastic lesions” were divided into those with “DALM’s” (16 patients) or adenomas (11
patients) based on the presence or absence of dysplasia in flat mucosa adjacent to the elevated lesions\textsuperscript{19}. Thus, most of the DALM’s in their study were non-adenoma like. Nevertheless, patients with DALM’s were significantly younger, had longer duration of disease, and had more extensive disease compared to patients with sporadic adenomas. Finally, in another retrospective case-control study by Schneider et al,\textsuperscript{18} 126 “circumscribed” lesions and 10 “large area” lesions in 76 patients with UC were classified into “adenomas” and “UC-related dysplastic lesions” on the basis of morphologic criteria, and then compared for their clinical features. In that study, lesions believed to be non-UC related had a significantly older age at the time of diagnosis, shorter disease duration, and a lower likelihood of having multiple polyps compared to patients with UC-related dysplastic lesions. However, this study was limited by the fact that the authors characterized all polypoid lesions as “adenomas” or “CUC” associated polypoid dysplastic lesions” based on predetermined and arbitrary histologic criteria. In summary, although certain gross and microscopic features are present significantly more often in UC-related adenoma-like DALM’S compared to sporadic adenomas, the sensitivity and specificity of these features are low. Therefore, they are not often helpful in reliably distinguishing these lesions in individual cases.

Attempts have also been made to separate UC-related adenoma-like DALM’s from sporadic adenomas by immunohistochemical or molecular methods\textsuperscript{20-27}. However, the studies that evaluated these parameters were all retrospective in design, and lack consistency in the criteria used for selection of cases into each of the two diagnostic categories. Nevertheless, based on the fact that recent molecular studies have suggested that the order and timing of genetic events may be different in CUC-related carcinogenesis compared to sporadic carcinogenesis, attempts have been made to utilize this information to help separate adenoma-
like DALM’s in UC from sporadic adenomas unrelated to IBD\textsuperscript{20-27}. For instance, CUC-related neoplasia shows early and frequent mutations in Kras, p53 and LOH of chromosome 17p, 9p and the Von Hippel Lindau gene (VHL 3p25) in contrast to sporadic carcinogenesis, which shows early genetic alterations in the APC gene and late mutations, or LOH, of the p53, CDC and VHL gene\textsuperscript{28,29}. In a retrospective case-control immunohistochemical study by Walsh et al, p53 and B-catenin expression was evaluated in 17 UC patients with adenoma-like DALM’s, 21 UC patients with sporadic adenomas and 13 non-UC controls with sporadic adenomas\textsuperscript{25}. The p53 and B-catenin expression patterns were similar in UC-associated sporadic adenomas compared to non-UC associated sporadic adenomas. However, UC-associated adenoma-like DALM’s showed a significant increase in the prevalence rate (29%), and degree, of p53 staining. “Strong” p53 reactivity was detected only in UC-associated adenoma-like DALM’s. In contrast, only 8% of UC-associated DALM’s showed nuclear B-catenin expression compared to 40% and 46% of UC-related and non-UC related, sporadic adenomas, respectively. Thus, the combination of strong p53 expression, and either absent or weak nuclear B-catenin expression, was evidence in favor of UC-related adenoma-like DALM’s. Unfortunately, the sensitivity of these diagnostic tests is too low to be of value as an initial screening tool to discriminate UC-related adenoma-like DALM’s from sporadic adenomas. In another study by Mueller et al, p53 and BCL-2 expression were evaluated in UC-related “adenomas” and UC-related “dysplasia” and compared to a sporadic adenoma control group\textsuperscript{24}. However, that study did not indicate the specific criteria used to distinguish “UC-related adenomas” from “UC-related dysplasia”.

Few studies have addressed specifically the molecular aspects of adenoma-like DALM’s versus non-adenoma like DALM’s using rigid endoscopic and pathologic criteria\textsuperscript{20,22,23,27}. Fogt, et al, compared a variety of genetic alterations, including LOH of the p53 and APC genes, in
UC-associated sporadic adenomas and UC-associated “flat” dysplasia by PCR\textsuperscript{22}. They found LOH for APC in 21% of 19 UC-related sporadic adenomas, but in none of the flat high-grade dysplastic lesions not associated with carcinoma. In contrast, LOH for p53 was detected in 50% of UC-associated dysplasia, although this parameter was not measured in sporadic adenomas in their study. In another study, this same research group evaluated genetic alterations in UC-related DALM’s (presumably non-adenoma like) compared to UC-related sporadic adenomas and showed that LOH of 3p was significantly more common in the former compared to the latter\textsuperscript{20}. However, a specific analysis, and comparison, of UC-related adenoma-like DALM’s to non-adenoma like DALM’s was not performed.

In the only published study to date that evaluated molecular abnormalities in UC-related adenoma-like DALM’s compared to sporadic adenomas, Odze et al evaluated LOH of 3p, APC and p16 in 21 UC- patients with an adenoma-like DALM, 8 UC patients with a non-adenoma like DALM and 23 patients with a sporadic adenoma in a retrospective case-control study\textsuperscript{21}. UC-associated non-adenoma like DALM’s showed a significantly higher rate of LOH of 3p (50%) and LOH of p16 (56%) compared to either UC-associated adenoma-like DALM’s or non-UC related sporadic adenomas. However, no statistical differences were detected in the frequency of LOH of 3p, APC, or p16 in UC-associated adenoma-like DALM’s located either within, or outside, areas of colitis compared to non-UC related sporadic adenomas. Based on this data, they concluded that UC-associated adenoma-like DALM’s have a similar molecular profile to non-UC related sporadic adenomas and, thus, may represent a similar pathogenetic entity.
Natural history and Treatment of Adenoma-like DALM’s

There is compelling recent data to suggest that UC patients with an adenoma-like DALM may be treated adequately by polypectomy and continued surveillance regardless of the underlying pathogenesis (whether UC-related or sporadic) of the lesion\textsuperscript{14,15}. In a recent long term prospective follow-up study of 34 UC patients who had a polypectomy and continued surveillance for adenoma-like DALM’s in UC, overall, 20 of 34 patients (58.8\%) developed at least one further adenoma-like DALM upon follow-up, but only 1 patient developed flat, low-grade dysplasia and only 1 other developed adenocarcinoma, after his/her initial polypectomy. Most importantly, there were no significant differences in the incidence of polyp formation, upon follow-up, between UC patients with an adenoma-like DALM (62.5\%) and UC patients with a known sporadic adenoma (50\%), or between either of these two UC patient groups and a non-UC sporadic adenoma control group (49\%). This study represents the long-term outcome results of a previously published study by the same research group that included, on average, about 3 years of follow-up\textsuperscript{16}. Another prospective cohort study by Rubin et al, showed dramatically similar results to the study by Odze et al\textsuperscript{15}. In their study, the outcome of 30 UC patients and 18 CD patients with 70 dysplastic polyps that resembled “adenomas” endoscopically and pathologically, all of which were treated by polypectomy with continued surveillance with a mean follow-up of 4.1 years, was evaluated. Most patients (52\%) did not develop any further polyps and none developed either flat dysplasia or adenocarcinoma. The results of one other small uncontrolled case series supports the findings of these two prospective studies summarized above\textsuperscript{30}. Furthermore, a recent study published only in abstract form (Kundu) suggests that the outcome of UC patients with adenoma-like DALM’s is not dependent on the degree of dysplasia in the lesion\textsuperscript{31}. 
As a result of these studies, a recently proposed treatment algorithm for UC patients with either an adenoma-like or a non-adenoma like DALM’s, has been proposed and is outlined in Table 3. Due to the high association of cancer with non-adenoma like DALM’s, which ranges from 38% to 83%, it is recommended that UC patients with a non-adenoma like DALM, regardless of the grade of dysplasia detected on biopsy analysis, should receive a colectomy because of the high association with metachronous, or synchronous, carcinoma. Adenoma-like DALM’s located outside, or proximal, to areas of known colitis may be assumed to be sporadic in origin and, thus, treated conservatively by polypectomy and continued surveillance. Similarly, adenoma-like DALM’s that are located within areas of known colitis may also be treated conservatively, by polypectomy and continued surveillance, if the lesion has been excised completely and shows an absence of dysplasia at the margins of the specimen, and there is no evidence of flat dysplasia elsewhere in the colon, either adjacent to, or distant from, the polypoid lesion. These recommendations may apply to UC patients regardless of their age, duration, extent of colitis or degree of dysplasia in the lesion. Although it is recognized that an adenoma-like DALM that occurs in a young patient (less than 50), with severe pancolitis, is more likely UC-related in comparison to the same type of growth in an older patient with shorter duration of disease, the results of the previously cited prospective studies suggest that these two types of lesions may be treated safely by polypectomy because of the low likelihood of developing flat dysplasia or adenocarcinoma upon long-term follow-up.

The basis of this treatment algorithm relies heavily on the capacity of endoscopists’ to adequately categorize elevated dysplastic lesions in UC as either adenoma-like or non-adenoma like. In a recent study by Farraye et al, 38 gastroenterologists (12 private practice, 13 academic, 13 IBD experts) were asked a series of questions on the diagnosis and management of UC-
associated polypoid lesions via an internet survey of 13 endoscopic images of DALM’s (5 adenoma-like DALM’s, 5 non-adenoma-like DALM’s, 3 inflammatory polyps). IBD experts showed a significantly higher proportion of correct diagnoses (75%) and interobserver agreement (K=0.64) compared to other gastroenterologists (53%, K=0.36). Given that treatment decisions are heavily influenced by the gross characteristics of the lesions, the results of this trial suggested that gastroenterologists need to be educated regarding objective endoscopic criteria that help separate adenoma-like from non-adenoma-like DALM’s. Nevertheless, regardless of the endoscopic appearance, published evidence suggests that UC-related polypoid dysplastic lesions that are amenable to removal by endoscopic resection may, in fact, be treated safely by this method. Thus, regardless of the ability of the endoscopist to accurately classify a polypoid lesion in UC as adenoma-like or non-adenoma like, the ability to remove the lesion completely by endoscopic methods is a more objective alternative method of determining whether a patient can be treated safely by polypectomy.
<table>
<thead>
<tr>
<th>Gross Features of DALM’s</th>
<th>Adenoma-like (endoscopically resectable)</th>
<th>Non-adenoma like*1 (endoscopically non-resectable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sessile/pedunculated</td>
<td>Usually sessile (broad based)</td>
<td></td>
</tr>
<tr>
<td>Well circumscribed</td>
<td>Poorly circumscribed</td>
<td></td>
</tr>
<tr>
<td>Smooth surface</td>
<td>Irregular surface</td>
<td></td>
</tr>
<tr>
<td>Visible borders</td>
<td>Indistinct border</td>
<td></td>
</tr>
<tr>
<td>Non-ulcerated</td>
<td>Ulceration/necrosis</td>
<td></td>
</tr>
<tr>
<td>No stricture</td>
<td>Stricture</td>
<td></td>
</tr>
<tr>
<td>No mucosal tethering</td>
<td>Tethering</td>
<td></td>
</tr>
</tbody>
</table>

*1 Includes velvety patches, irregular, plaques, nodules or bumps, wart-like thickening
Table 3. Proposed Management Scheme for DALM’s in IBD

DALM

Adenoma-like

Outside colitis

• Polypectomy
• Regular surveillance

Inside colitis

• Polypectomy

Non Adenoma-like

• Confirm absence of flat dysplasia and negative margins
• Regular or increased surveillance

Colectomy
References


17. Friedman S, Odze RD, Farraye FA. Management of Neoplastic Polyps in Inflammatory Bowel Disease. Inflammatory Bowel Diseases 2003;9:260-266


