

## Diagnosis and Management of Polyps in Inflammatory Bowel Disease

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### Introduction

The majority of polyps in inflammatory bowel disease (IBD) are inflammatory. Hyperplastic, mesenchymal, lymphoid, and a variety of other polyps may also occur in IBD, but less commonly. However, most of the polyps in these other categories do not necessarily show an increased prevalence in IBD, but instead develop coincidentally in association with IBD. Epithelial polyps associated with IBD are mainly dysplastic, and as a result, pose a difficult diagnostic dilemma regarding their separation from sporadic neoplastic lesions. This lecture will concentrate mainly on lesions with an increased frequency in IBD.

### Inflammatory Polyps

#### A. Usual Type

Inflammatory polyps (or “pseudopolyps”) are the most common type of polyp in IBD. They represent polypoid areas of inflamed and regenerating mucosa that project above the level of the surrounding mucosa, the latter of which may be ulcerated. They occur most commonly in patients with moderate to severe colitis, but persist in patients with quiescent disease, and may also occur in association with the other inflammatory disorders of the GI tract, such as ischemic colitis or infectious colitis<sup>1-2</sup>. Overall, they are believed to develop as a regenerative response to localized, or diffuse, inflammation and ulceration of the mucosa followed by regeneration of the intervening non-ulcerated epithelium. Eventually, the regenerated mucosa becomes completely re-epithelialized and persists above the level of the surrounding mucosa, even when the latter has healed completely. However, some inflammatory polyps may simply represent residual islands of spared mucosa surrounding areas of deep ulceration, and it is these types of lesions that have been referred to as “pseudopolyps” by some.

Grossly, inflammatory polyps may be sessile or pedunculated but may assume almost any shape. For instance, some may be worm-like or consist of long finger-like projections, often referred to as filiform<sup>3-4</sup>. They may be single, multiple or numerous in number, and usually range in size from 0.5 to 1.0 cm. However, some polyps may grow to an extremely large size (“giant” inflammatory polyp), which can result in bleeding, obstruction, prolapse or intussusception<sup>5-9</sup>. Endoscopically, most inflammatory polyps

have a smooth hyperemic/hypervascular appearance with or without surface erosion, and tend to bleed when manipulated. Their appearance is usually easily distinguishable from neoplastic polyps. Histologically, inflammatory polyps are composed of a mixture of inflamed lamina propria and distorted colonic epithelium consisting of tortuous, branched, elongated and cystic crypts. Surface erosion, congestion, hemorrhage, and crypt abscesses may also be present.

The vast majority of inflammatory polyps are benign, innocuous lesions, which do not cause any significant complications. Occasionally, as mentioned above, particularly in severe cases of IBD, numerous inflammatory polyps with long finger-like projections (filliform polyposis), may develop, particularly in the distal colorectum, and cause obstructive symptoms<sup>3,4,8</sup>. The main clinical issue in patients with filliform polyposis is the difficulty in monitoring their progression, separating purely inflammatory ones from those with dysplasia, and performing regular biopsy surveillance. As a result, most patients with extensive filliform polyposis are treated by colectomy. Some inflammatory polyps develop markedly enlarged, spindle or epithelioid shaped, multi nucleated, bizarre stromal cells that mimic sarcoma. These are referred to as pseudosarcomatous changes, and occur most often at the surface of the polyp, particularly in those that are ulcerated<sup>10</sup>. These cells can be distinguished from sarcoma by the lack of atypical mitoses, their location preferentially underneath areas of ulceration within a granulation tissue reaction, and their frequent positivity for endothelial, or myofibroblast, phenotypic markers.

Rarely, dysplasia or even carcinoma, may develop in inflammatory polyps<sup>11-12</sup>. The histologic features are similar to dysplasia or carcinoma that develops in flat mucosa in IBD. However, inflammatory polyps do not carry a significantly increased risk of dysplasia above that of the surrounding mucosa, and, thus, are not considered pre-neoplastic lesions.

The natural history of inflammatory polyps is unclear. Some polyps decrease in size, most remain stable and few may continue to grow, particularly if they undergo torsion or prolapse. Treatment is generally directed at the underlying inflammatory condition. However, large, or numerous, polyps are often excised to rule out dysplasia. Inflammatory polyps with dysplasia should be managed similar to dysplasia in flat mucosa.

## B. Inflammatory Cap Polyps

Some inflammatory polyps in IBD may develop either primarily, or secondarily, as a result of peristalsis or trauma induced mucosal prolapse<sup>13-16</sup>. This may result in traction, distortion and twisting of the polyp which can lead to localized ischemic damage, regeneration and repair of the lamina propria and epithelium and the development of an inflammatory polyp. Cap polyps are defined as an inflammatory polyp, either with or without prolapse-related changes, that contain an overlying “cap” of necroinflammatory debris and granulation tissue<sup>14</sup>. Cap polyps are usually isolated lesions, but they can be numerous in number which can lead to bleeding, obstruction, or rarely, hypoproteinemia<sup>9,14,16</sup>. Most cap polyps occur in the rectosigmoid region on the crest of

mucosal folds. Most are less than 1.0 cm in size. Other types of mucosal prolapse polyps, without a cap of granulation tissue, may also develop in IBD, but are less common.

### C. Colitis Cystica Polyposa/Profunda

This is a rare benign condition characterized by misplacement of mature, often architecturally distorted or cystically dilated, crypts through the muscularis mucosa into the submucosa or deep layers of the bowel wall<sup>17-19</sup>. This condition occurs more commonly in patients with solitary rectal ulcer syndrome, but may also occur, rarely, in patients with IBD, particularly Crohn's disease. In IBD, colitis cystica polyposa/profunda (CCP) may be either localized or diffuse. The pathogenesis of CCP in IBD is believed to occur as a result of repeated bouts of ulceration followed by repair of the mucosa and entrapment of epithelium. Histologically, in addition to the typical features of IBD in the overlying and surrounding mucosa, CCP may show cystically dilated, architecturally distorted, mucin-filled crypts in the submucosa, muscularis propria, or serosa<sup>19</sup>. The crypts may be entirely normal in appearance or may show marked regenerative changes which, on occasion, may be difficult to distinguish from well-differentiated adenocarcinoma. However, in contrast to adenocarcinoma, misplaced crypts in CCP often grow in a lobular configuration, are not associated with desmoplasia, and are often surrounded by a discrete rim of lamina propria. Misplaced crypts may also show mucin depletion, pseudostratification, and hyperchromaticity of the nuclei. However, loss of polarity, atypical mitoses, and intraluminal necrosis are not features of this disorder. Some cases may show extensive hemorrhage, congestion and hemosiderin deposition. The treatment of CCP depends primarily on the mode of clinical presentation. Most cases are resected due to the difficulty in distinguishing this condition from carcinoma from a clinical, radiological or pathological point of view, or because of intraluminal obstruction. IBD-related CCP does not carry an increased risk of neoplastic change.

### Hyperplastic polyps

Hyperplastic polyps may occur in patients with IBD and are usually morphologically similar to those that occur in non-IBD patients<sup>21</sup>. They may occur in inflamed or normal appearing mucosa. In a study by our group, the molecular characteristics of 39 hyperplastic polyps from 26 ulcerative colitis (UC) patients were compared to 39 sporadic hyperplastic polyps from patients without UC<sup>21</sup>. Most polyps (92%) were located within an area of established colitis, and in the left colon (82%). Polyps ranged in size from 0.1-1.4 cm in diameter (average: 4.3 mm). Forty-seven percent of UC-associated hyperplastic polyps showed a molecular abnormality, such as LOH of APC (21%), 3p (40%), p53 (27%), or p16 (20%). However, the frequency of molecular abnormalities was similar to sporadic hyperplastic polyps, which suggested that UC-associated hyperplastic polyps are biologically similar to the sporadic type. Nevertheless, the finding of molecular abnormalities in these lesions supports the theory that these lesions may have neoplastic potential which is probably unrelated to the

underlying IBD. Interestingly, non-polypoid flat hyperplasia-like mucosal changes has also recently been described in Crohn's disease by Kilgore et al<sup>22</sup>. In a morphological and p53 immunohistochemical study of 30 cases of Crohn's-related adenocarcinoma and 38 age and sex matched cases of Crohn's disease without adenocarcinoma, hyperplastic mucosal changes were present in 33% of the former and 10% of the latter. These changes were characterized by a "diffuse expanse of flat mucosa with an architecture resembling that seen in colorectal hyperplastic polyps and composed of cells with cytologically bland basal nuclei and apical cytoplasmic mucin distention". These features were noted both adjacent to and distant from adenocarcinoma. Fifty percent of cases showed p53 immunoreactivity. The authors of that study suggested that this may represent a distinct type of dysplastic change, but this is yet to be confirmed. A similar type of "villous mucinous mucosa" has recently been described in long-standing UC by Anderson et al in 1999<sup>23</sup>. These investigators showed a high frequency of K-ras mutations in this type of epithelium (61%), which was more frequent than low-grade dysplasia. However, it is unclear if the type of epithelium evaluated in the study by Anderson et al is the same as the one evaluated by Kilgore et al.

The natural history of hyperplastic polyps in IBD is unknown, and the treatment of these lesions is similar to patients without IBD. Clinically, hyperplastic polyps may be difficult to distinguish from small elevated polypoid areas of dysplasia and, thus, are often excised for diagnosis.

## **Epithelial**

### **A. General comments and classification**

Elevated or raised areas of dysplastic epithelium occurs, not uncommonly, in patients with IBD<sup>1,12,24</sup>. By convention, raised dysplastic areas have been referred to as a dysplasia associated lesion or mass (DALM)<sup>12</sup>. However, there are, in fact, several different subtypes of DALM's in IBD. These subtypes are broadly separated into adenoma-like and non-adenoma like based primarily on their gross endoscopic appearance, and are managed quite differently. Examples of non-adenoma like lesions are large, sessile, irregular masses, strictures or ill-defined nodules with a broad base. A biopsy finding of dysplasia, either low or high-grade, in a non-adenoma like DALM is usually an indication for colectomy because of the high probability of an associated adenocarcinoma. In fact, many studies have shown a carcinoma prevalence rate from 30-80% in patients with lesions of this kind<sup>12,24</sup>. More commonly, isolated, well-circumscribed, sessile or pedunculated adenoma-like polypoid dysplastic lesions develop in patients with IBD. In this instance, the clinical differential diagnosis includes an adenoma-like DALM in UC, a lesion that is pathogenetically linked to the underlying inflammatory disorder, versus a sporadic adenoma, a lesion that occurs coincidentally in a patient with underlying IBD, but is unrelated to it from an etiologic point of view. This distinction is important because the former type of lesion is generally considered an indication for colectomy in medically fit patients, due to a high rate of progression to adenocarcinoma, whereas the latter is normally treated by a polypectomy, similar to a

sporadic adenoma in a patient without IBD. Thus, a common diagnostic dilemma for both clinicians and pathologists is how to differentiate these lesions. Fortunately, recent data, primarily based on the results of two follow-up studies, suggests that IBD patients with an adenoma-like DALM, regardless of whether it is determined to represent a sporadic or an IBD related lesion, may be treated adequately by polypectomy and continued surveillance if there is no evidence of flat dysplasia elsewhere in the patient<sup>25,26</sup>. This is discussed further below. Nevertheless, there are a variety of features that can be used to help distinguish these lesions, which are outlined in the next section.

## B. Pathologic features and differential diagnosis

Non-adenoma like and adenoma-like DALM's may look identical histologically. Therefore, distinction between these two types of lesions is based solely on their gross endoscopic appearance and will not be discussed further. Adenoma-like lesions that occur proximal to histologic areas of colitis (i.e. right sided lesion in a patient with left sided UC) can easily be diagnosed as a sporadic adenoma because it is well known that dysplasia related to IBD develops only in areas involved by the inflammatory process. However, adenoma-like lesions that occur within areas of colitis are more difficult to distinguish from true polypoid dysplastic lesions related to the underlying colitis<sup>27,28</sup>. IBD-associated lesions generally occur in younger patients (usually less than 60 years of age), with pancolitis for at least 10 years duration<sup>27</sup>. These polyps are located more commonly in the left colon and are often associated with areas of flat dysplasia either near or distant from the polyp. Histologically, IBD-related lesions usually show an increase in the amount of lamina propria and crypt inflammation, and may even show crypt abscess's involving dysplastic epithelium. In a previous study by our group, a mixture of benign dysplastic inflamed crypts at the surface of the polyp was found more commonly (60% of cases) in IBD related lesions in contrast to sporadic adenomas (16%)<sup>27</sup>. In addition, flat dysplasia is often detected at the base of the polyp stalk, and in the mucosa surrounding the polyp. Thus, stalk dysplasia should alert the pathologist that the polyp is likely to be an IBD-associated lesion, rather than a sporadic adenoma, and should prompt a search for dysplasia elsewhere in the colon. Features such as polyp size, architectural type, and degree of dysplasia, as well as nuclear cytologic features, are not helpful in distinguishing these two groups of lesions. Interestingly, one recent study by Rubio et al suggested that the majority of "adenomatous growths" juxtaposing IBD-associated carcinomas have a villous or serrated morphologic growth pattern, but the significance of this finding is unclear.<sup>29</sup>

By immunohistochemistry, IBD-associated adenoma-like DALM's have a higher degree of p53, and a lower degree of nuclear beta-catenin, staining in contrast to sporadic adenomas<sup>30</sup>. Although several other studies have evaluated immunohistochemical findings in these two groups of lesions, none have shown to be particularly useful in this differential diagnosis<sup>31,32</sup>. For instance, the expression of Glut-1, or hMLH1 and hMSH2, show a similar degree and type of staining in DALM's versus sporadic adenomas<sup>31,32</sup>.

## C. Molecular features

There are well known differences in the type, prevalence and timing of certain molecular events in the pathogenesis of IBD (particularly UC)-associated neoplasia compared to sporadic colon carcinogenesis<sup>12,21,24,33-34</sup>. For instance, UC associated neoplasms demonstrate infrequent and late mutations in the APC and beta-catenin genes, but show frequent early abnormalities in the 3p, p53, p27, and p16 genes in comparison to sporadic adenomas. Based on this information, several investigators have evaluated and compared the molecular findings in DALM's, some of which included pathogenetically distinct groups of adenoma-like lesions, to sporadic adenomas in an effort to help distinguish these two types of lesions<sup>28,33-35</sup>. For instance, Fogt et al showed that LOH for p16 (9p), 17p (p53) and 3p were statistically more common in adenoma-like polypoid dysplasia compared to sporadic adenomas<sup>35</sup>. LOH of p16, 17p and 3p were present in 35%, 16% and 50% in the former compared to 0%, 10% and 0% of the latter, respectively. A study by our group, in 2000, evaluated LOH of 3p, APC and P16 by PCR analysis in 21 UC patients with an adenoma-like DALM, and compared the results to 8 UC patients with a non-adenoma like DALM, and 23 non-UC patients with a sporadic adenoma<sup>34</sup>. Interestingly, adenoma-like DALM's in UC had a statistically similar molecular profile to sporadic adenomas. For instance, LOH of 3p, APC and p16 were noted in 25%, 30%, and 5% of UC-related adenoma-like DALM's compared to 5%, 33%, and 4% of non-UC related sporadic adenomas. Furthermore, lesions that occurred either within or outside areas of chronic colitis had a similar molecular profile. However, in contrast, non-adenoma like DALM's showed a significantly higher frequency of LOH of 3p and p16 (50% and 56%, respectively) indicating that, perhaps, a different pathogenetic molecular sequence of events occurs in adenoma-like versus non-adenoma like DALM's in UC. Thus, although subtle molecular differences may exist between IBD and non-IBD related lesions, at this point, distinguishing groups of DALM's by molecular analysis remains an investigational tool.

Recently, Selaru et al evaluated the ability of artificial neural networks (ANNs), based on complementary DNA (cDNA) microarray technology, to discriminate between IBD and non-IBD related cancers<sup>36</sup>. Use of this technology correctly diagnosed 12 blinded samples (3 IBD cancers and 9 sporadic cancers) in a test set indicating that this methodology may have great potential to discriminate among different types of dysplastic lesions in the future. Unfortunately, this study did not compare adenoma-like lesions in IBD to sporadic adenomas.

#### D. Natural history and Treatment

There is recent strong evidence to suggest that adenoma-like DALMS, regardless of their particular etiology (i.e. whether they represent an IBD-related or a sporadic lesion) may be treated conservatively with polypectomy and continued endoscopic surveillance, instead of colectomy<sup>25,26,37</sup>. In a study by our group of 24 UC patients all of whom had a polypectomy followed by surveillance for an adenoma-like DALM, 58% of patients developed further adenoma-like lesions upon 3.5 years of follow-up, but only 1 patient developed an isolated focus of low-grade dysplasia and none developed carcinoma<sup>25</sup>. These results were strikingly similar to a control group of non-UC patients with a sporadic adenoma who had a statistically similar frequency of recurrent polyp formation

when treated in a same manner. In an abstract presented by our group at the current USCAP meeting, the same cohort of patients noted above were followed for a longer period of time (average: 8 years)<sup>37</sup>. Although, overall, 62% developed further adenoma-like lesions, which, once again, was similar to the non-UC control group, no other patients developed flat dysplasia and only one patient (4%) developed adenocarcinoma 7.5 years after his/her initial polypectomy. Strikingly similar results were found by Rubin et al in a follow-up study of dysplastic polyps in 48 IBD patients with a mean of 4.1 years of follow-up<sup>26</sup>. In their study, none of the patients developed dysplasia or carcinoma in flat mucosa upon surgical resection or follow-up colonoscopy. Based primarily on the results of these two studies, a preliminary management scheme for patients with adenoma-like and non-adenoma like DALM's in UC has been recommended (see Figure 1 for details). However, it is important to remember that the treatment plan outlined in Figure 1 depends heavily on the endoscopic appearance of the lesion in question, and is based on the premise that there is no evidence of flat dysplasia in other areas of the patients colon by colonoscopic biopsy analysis. Regardless of the presence of an adenoma-like dysplastic lesion, any IBD patient who has one or more areas of flat dysplasia should be considered a candidate for colectomy.

### **Mesenchymal Polyps**

A wide variety of mesenchymal polyps have been reported, anecdotally, in both Crohn's disease and UC, but none have shown a predilection to occur with increased frequency in either of these two conditions<sup>38-39</sup>. The pathologic features of these lesions are similar to those that occur outside the setting of IBD and, thus, will not be described here. However, of the numerous types of lesions that have been described, inflammatory fibroid polyps are the most common<sup>40</sup>. These lesions have been described in Crohn's disease and UC, as well as in continent ileo-anal pouches after colectomy. Another extremely rare form of mesenchymal polyp that has recently been described in Crohn's disease is nodular neuronal hyperplasia<sup>39</sup>. This proliferation may occur as an isolated lesion, or in association with an inflammatory polyp. Finally, fibroepithelial polyps may occur in the perianal area in patients with Crohn's disease, and are believed to develop as a result of chronic repeated injury<sup>38</sup>.

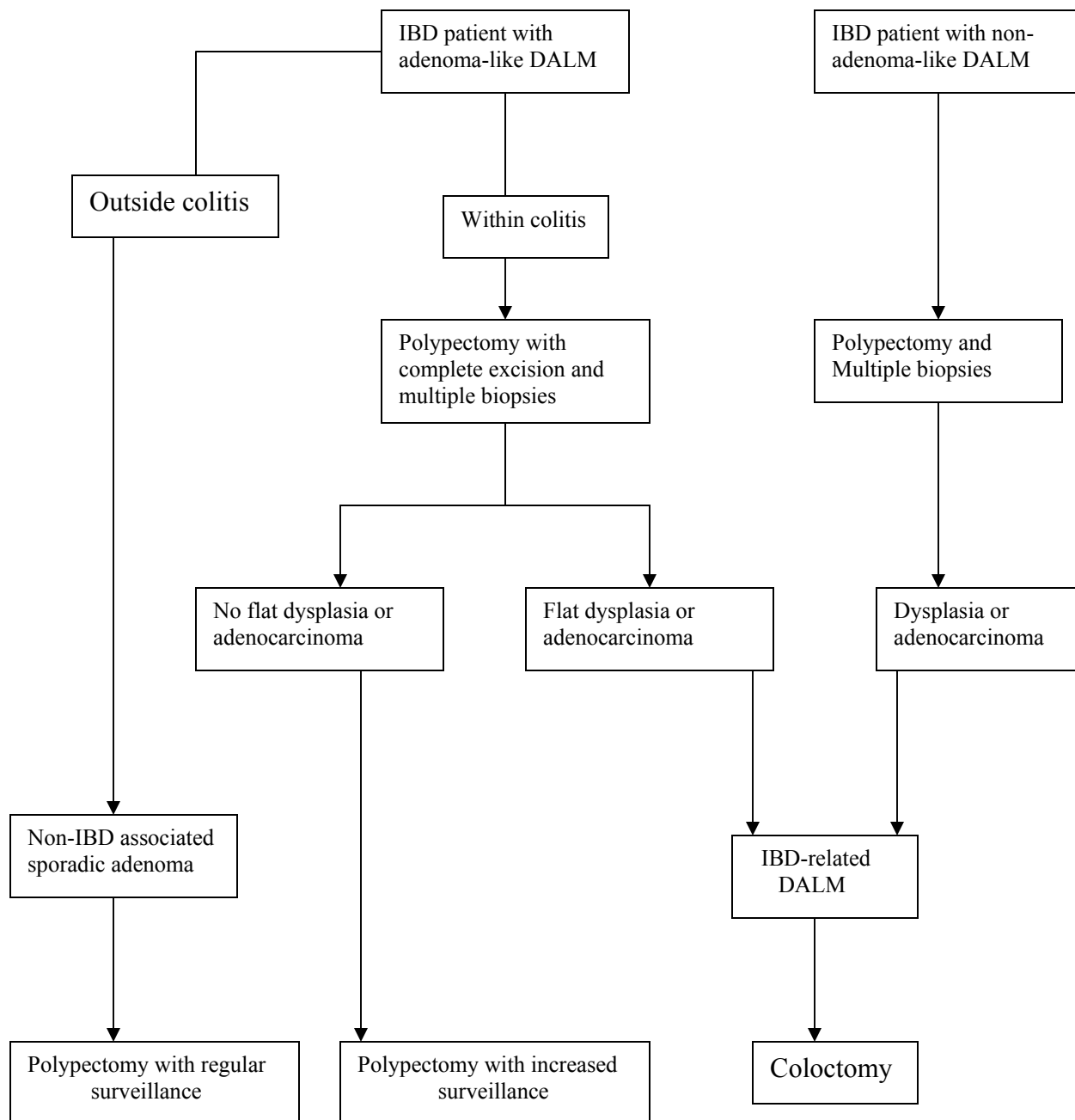
### **Lymphoid Polyps**

Benign hyperplastic lymphoid nodules are, by far, the most common type of lymphoid polyp associated with IBD. Lymphoid hyperplasia is most common in the rectosigmoid region but may be particularly prominent, and diffuse, in segments of ileum or colon that have been diverted from the fecal stream, even in patients with IBD.

Non-Hodgkin's lymphoma is an extremely rare complication of IBD, but often presents as a polypoid lesion or mass<sup>41-43</sup>. In one series of 117 GI lymphomas, only one arose in a patient with UC<sup>43</sup>. However, in other studies, from 3-15% of colorectal lymphomas occur in UC patients<sup>41-46</sup>. Although the association of lymphoma with IBD is

controversial, most authorities believe that the risk is slightly increased<sup>47-51</sup>. The increase in risk may occur primarily, but is more likely due to the effects of immunosuppressive drugs, such as anti-TNF, azothiaprime, 6-MP and cyclosporin<sup>47-52</sup>. In a recent report, the incidence of lymphoma was increased, and the interval to the development of lymphoma was decreased, in UC patients who were treated with immunosuppressive drugs compared to older reports<sup>52</sup>. Lymphomas associated with UC more commonly occur within the bowel, but may occur in surrounding lymphoid tissue as well. Within the bowel, they are almost always found in areas of active inflammation, are more often multiple, and occur more frequently in the distal colon, in contrast to non-IBD related GI lymphomas<sup>45-46</sup>. Histologically, they are often high grade, mostly of the diffuse large B cell type<sup>52</sup>. However, rare cases of low or high-grade polymorphic B cell lymphoma, marginal zone B cell lymphoma, and even T cell lymphoma, may occur as well<sup>42,46,53</sup>.

Only a handful of lymphomas have been reported in Crohn's disease<sup>52</sup>. Rarely, primary intestinal Hodgkin's disease, some related to EB virus infection<sup>52</sup>, may develop in association with IBD, particularly Crohn's disease<sup>54,55</sup>. Finally, some cases of malignant lymphoma of the colon may present with symptoms and signs simulating IBD, but in these cases, the affected patient does not actually have the inflammatory disorder<sup>56-57</sup>.

**Figure 1. Treatment of DALMs in IBD**

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