Carcinoma in inflammatory bowel disease: endoscopic advances, management, and specimen handling. A review for the pathologist

Michael Vieth
Raja Atreya
Helmut Neumann

Abstract

Inflammation plays a major role in the development of carcinomas in IBD. The previous role of stromal cells has probably been underestimated in the past. In general treatment regimens aim to reduce the inflammation to prevent carcinoma. Endoscopy and histopathology play a major role not only in diagnosis of neoplasia but also in removal and staging and have to follow strict steps to ensure high quality. At our institution about 90% of all carcinomas in IBD are cases of ulcerative colitis. Therefore, we focus on the present manuscript more on ulcerative colitis rather than carcinoma in Crohn's disease. Sometimes outside from specialized centres partial colectomies are carried out in cases with carcinomas in ulcerative colitis instead of performing complete proctocolectomies. Our retrospective data show that there is a higher risk for relapses from lymph node metastasis but also for metachronous lesions. The survival rates are almost comparable but complete colectomies are still the treatment of choice for carcinomas in ulcerative colitis.

Keywords carcinoma; Crohn's disease; histology; treatment; ulcerative colitis

Introduction

There is an increased incidence of colorectal cancer (CRC) in patients with ulcerative colitis and Crohn's disease, which depends on the severity of mucosal inflammation and the extent and duration of the disease.[1,2] The molecular mechanisms that contribute to the progress from mucosal inflammation towards the development of colitis-associated cancer (CAC) are not fully elucidated, but clearly differ from the adenoma-carcinoma sequence in sporadic CRC. The microbial flora and regional mucosal differences concerning structure and cellular composition are involved in the neoplastic process.

Michael Vieth *MD PhD Head, Institute of Pathology, Klinikum Bayreuth, Bayreuth, Germany. Conflicts of interest: none declared.*

Raja Atreya *MD PhD Head of IBD Unit, Department of Medicine I, University Hospital Erlangen, Erlangen, Germany. Conflicts of interest: none declared.*

Helmut Neumann *MD PhD Head of Molecular Endoscopy Unit, Department of Medicine I, University Hospital Erlangen, Erlangen, Germany. Conflicts of interest: none declared.*

A recent study describes an elevated expression of epiregulin (EREG), a member of the Epidermal Growth Factor (EGF) family, in mouse models for CAC but not in sporadic CRC.[3] Correspondingly, augmented expression could also be found in ulcerative colitis patients with colitis associated neoplasms as compared with sporadic neoplasms. Tumour-associated fibroblasts were the key cellular source of EREG in CAC. Functional studies proved that EREG is an epithelial growth factor that specifically promotes tumour growth independent of the mucosal inflammatory process. The proliferation of intestinal epithelial cells and thus tumour development by EREG requires previous Extracellular Signal-Regulated Kinase (ERK) activation. Therefore, the EREG/ERK signalling pathway seems to be highly relevant for inflammation-associated colorectal tumours.[3]

Besides these latest molecular insights some decades ago the diagnosis of carcinoma in IBD was remarkably easier. Most patients with various degrees of neoplasia were operated since it was known that cases with even low grade dysplasia harboured a carcinoma at least in 40% of all these cases.[4] The recommendations for histopathological workup were very clear: an operation specimen had to be documented, all visible lesions had to be embedded and step sections within the rectum at 5 cm steps and above the rectum in 10 cm steps had to be taken.[4,5] These procedures enable the pathologist still today to detect most of the neoplastic foci within a colectomy specimen.

Nowadays the situation has become more difficult as illustrated by a recent consult case: various hospitals try to lower costs by involving the pathology lab that offers the lowest price. This leads to the absurd situation where surgeons deliver high quality work but specimens with multifocal high grade dysplasia (HGD) and low grade dysplasia (LGD) with high risk for harbouring carcinoma are diagnosed somewhere outside specialized pathology reference centres. Accordingly, the recent case was just described as: "*117 cm long colectomy specimen in ulcerative colitis with attached 11 cm terminal ileum, five random sections have been embedded, upper and lower margin free of dysplasia*". After asking for the previously described focus of high grade dysplasia, the answer was that it is not possible to workup a 117 cm long specimen completely and that the low and high grade dysplasia diagnoses have been confirmed already in biopsies prior to the operation and since there is no carcinoma it means that no lymph nodes have to be examined. Interestingly, the surgeon did not complain about the diagnosis; it was the gastroenterologist who forced the pathologist to ask for a second opinion. The second opinion showed also no neoplasia since it came up to attention that the whole specimen (128 cm in length) was worked up in five paraffin blocks, only. The initial pathologist commented that the multifocal HGD and LGD diagnoses done at another institution have already been confirmed by others since they routinely ask for an outside second opinion in IBD cases. The point that HGD in ulcerative colitis is often an indicator that a carcinoma is already present, especially when there is multifocal HGD, was not accepted by the local pathologist. The climax of the story ended in a second report by the pathologist stating that the HGD and LGD foci are probably located somewhere else in the specimen but their (own few) sections are not representative. The gastroenterologist forced the pathologist to workup the specimen more properly, which led to another 50 paraffin blocks showing multifocal LGD and HGD but fortunately no carcinoma.

To avoid such stories all pathologists should be aware of how to deal with specimens of patients with IBD even if there is no suspicion for neoplasia. The worst part of this story is that one can bet that this is not the first time this particular surgeon accepted such way to workup a specimen by his pathologist. The consequences are clear: if patients are not properly diagnosed they may not get proper therapy, nor follow-up after an operation and this will not pop up within the next 2–3 years but it will become evident within a 5 year interval when hospitals have to calculate their specific survival rates, mortality rates, etc. and are getting forced to publish the results in the future.

During the last decades endoscopic imaging techniques improved and also the histological criteria are more widespread and more refined. It was noted by that sub differentiation in LGD and HGD can be made more reliable with precise description of such criteria.[6,7] Furthermore, the widespread use of biologicals to modulate the disease course rather than unspecifically suppress the immune system led to the situation that pathologists need to be more aware of drug induced changes.

Endoscopic diagnosis

Dysplastic lesions in IBD are often ill-defined and flat. Therefore, national and international guidelines recommend surveillance colonoscopy starting 8–10 years after the onset of symptoms and every 1–2 years after that in extensive colitis.[8] However, it is well accepted that white-light endoscopy is not sufficient enough to detect subtle dysplastic changes associated with IBD. Therefore, multiple biopsies, with a minimum number of 32 should be performed at each surveillance colonoscopy. The biopsy protocol should follow strict rules, including four-quadrant biopsies every 10 cm with placement in separate jars and targeted sampling of macroscopically suspicious lesions.[8] Within recent years, increasing efforts have been made to implement advanced endoscopic imaging techniques to endoscopic surveillance protocols in IBD.[9–11] In this context, various studies have shown the beneficial effect of dye-based chromoendoscopy for lesion detection in IBD.[12] It has been estimated that methylene blue guided chromoendoscopy yields in a 2.2-fold increased detection of dysplasia in ulcerative colitis, particularly by enhancing the detection of non-polypoid lesions.[13] Similar results have also been demonstrated for intravital staining using indigo carmine.[14] A recent meta-analysis of six randomized controlled trials demonstrated a pooled sensitivity, specificity and diagnostic odds ratio of 83%, 91% and 17.5, for dysplasia detection in long-standing UC by using dye spraying as compared to white-light endoscopy.[15]

Most recently, dye-less chromoendoscopy techniques become more widely available in most endoscopy units. Dye-less chromoendoscopy refers to optical and digital chromoendoscopy techniques, which are embedded into the video endoscope or the video processor and enabled by pushing a button on the handle of the endoscope.[16] Those techniques include Narrow Band Imaging (NBI; Olympus, Tokyo, Japan), Compound Band Imaging (CBI, Aohua, Shanghai, China), FICE (Fujinon Intelligent Color Enhancement or FICE, Fujifilm, Tokyo), i-scan (Pentax, Tokyo, Japan) and SPIES (Storz Professional Image Enhancement System, Storz, Tuttlingen, Germany). Although various trials have evaluated the potential benefit of dye-less chromoendoscopy for surveillance in IBD, the current literature does not fully support the use over traditional dye-spraying. Therefore, when available, dye-spraying should still be performed in surveillance colonoscopy to improve lesion detection. Very recently, the SCENIC international consensus statement on surveillance and management of dysplasia in IBD has been introduced.[17] Therefore, a panel of experts developed a set of terms for colonoscopic findings in IBD surveillance to establish uniformity in communication. It was agreed that the terms DALM and ALM should be abandoned and that the PARIS classification should be used to describe lesions as elsewhere in the GI-tract. The term endoscopically resectable indicates distinct identification of lesion margins and complete endoscopic removal is feasible. Complete removal has to be documented by obligate histological workup. Moreover, biopsy specimen taken adjacent to the resection site should be free of dysplasia on histology. The consensus recommends differentiation in endoscopically visible and invisible dysplasia. Visible dysplasia is divided into (I) polypoid (i.e. pedunculated and sessile lesions), and (II) non-polypoid (i.e. superficial elevated; flat; depressed) lesions. Moreover, the consensus highlights the use of dye-based chromoendoscopy for detection of dysplasia on surveillance in IBD.[17]

Due to the improvements of endoscopic imaging techniques detection of early carcinomatous lesions in IBD is becoming more and more frequent. Guidelines have allowed for endoscopic removal of focal lesions. However, some issues have to be kept in mind with regard to endoscopic resection of IBD related lesions:

- In cases of IBD carcinoma, outside specialist centres, partial colectomies instead of ileoanal pouch anastomosis are the method of choice
- It needs to be questioned whether partial colectomy is an alternative and whether focal endoscopic resection of neoplastic areas has to be considered as well.

Without any doubt there are cases that need to be operated since endoscopic follow-up is not possible due to severe, inflammation not responsive to treatment or numerous post-inflammatory polyps.[18]

Rational therapeutic management of inflammatory bowel diseases

The major aim of a rational medical therapy in IBD patients is the induction and maintenance of a steroid-free remission[19] and thus lowering the risk of developing carcinomas. The medical therapy depends on the severity, activity and extent of the disease and also takes into account the disease course of the patient. Treatment decisions are also influenced by comorbidities, extra-intestinal manifestations and previous therapies of the patient. Therapeutic algorithms can therefore only serve as a guideline and have to be adapted to the individual patient situation.[20,21] The rational therapeutic management should be based on a time-structured approach of the therapeutic options to prevent unnecessary delay of therapy and disease progression which often results in debilitating structural changes of the mucosa.[22] Mucosal healing represents another important prognostic therapeutic aim, as it has been shown to be associated with sustained clinical remission, lower rates of hospitalization and resection-free survival of IBD patients.[23] Before intensifying