Pitfalls in the Reporting of Neoplastic and Pseudo Neoplastic Lesions in the Colon and Rectum

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Abstract

Introduction: Colonic biopsies comprise large portion of pathologists’ daily work. Within various pathological entities, there are histological ranges and variations. Unawareness of all of these variabilities might lead to misdiagnosis by an inexperienced pathologist and, accordingly, to mismanagement.

Aim: The aim of this article was to alert the reporting pathologist to some of the most common and/or important pitfalls in considering a diagnosis of neoplastic conditions of the colon.

Materials and methods: We highlighted main neoplastic pitfalls in colonic biopsies histopathological investigations.

Results: The pitfalls described in this article are the most common problems we encountered according to our experience. Thus, double reporting for difficult cases is highly recommended to avoid problems in reporting such cases.

Conclusions: Pathologist should be fully alert when reporting some of the most common pitfalls.

Keywords

colonic biopsies, histopathology, neoplasm, pitfalls

INTRODUCTION

Ever since colonoscopies became widely used, the number of colonic biopsies has escalated to form not only a significant part of the general histopathologist’s workload, but also probably the major part of the gastrointestinal pathologist’s burden. Often, these biopsies have such significant diagnostic importance that clinical judgment is now almost totally reliant on the offered histopathological diagnoses. There are, however, some limitations in assessing biopsies in this way, as well as there are some pitfalls which the general pathologist may fall into that could lead to serious mismanagement.

Dysplasia: diagnosis, observer-variation and mimic

Dysplasia is defined as the premalignant condition characterised by a spectrum of abnormal cytological, architectural, and mutational changes. In the colon and rectum, the terminology was first popularised by Riddell et al. in 1983 when identifying such lesions in inflammatory bowel disease.[1] Based on the morphological changes, they divided dysplasia into three broad categories, namely negative, indeterminate, and positive for dysplasia. Positive is further subdivided into low and high grades. This recognition, al-
though built on solid, well-defined histopathological criteria, is still by and large a subjective opinion that lends itself to interobserver variation. In our experience, there is little difficulty in recognising the difference between absent for dysplasia on one end of the spectrum from high-grade dysplasia on the other end. The difficulty lies in distinguishing between the indefinite and the low-grade dysplasia. We found that many pathologists overuse the term indefinite for dysplasia due to three factors: small unrepresentative biopsies; badly orientated specimens; or reflection for a lack of confidence by the reporting pathologists. We strongly recommend sticking to strict, well-laid out histopathological criteria. Despite the approved criteria, Dixon et al.\cite{2} reported a disturbingly significant interobserver variation on high grade dysplasia. Due to the huge clinical significance of such a diagnosis, they suggested that such biopsies need to be reported by two pathologists, with one of them having a special interest in such lesions.\cite{2} Such a practice has become routine in UK. In our referral practice or during the Multi-Disciplinary Team Meetings (Tumour Board), we have downgraded diagnoses of low-grade dysplasia reported by general pathologist without support from GI pathologist. We have also seen colectomies based on experience. Features of reactive atypia include enlarged and stratified nuclei, along with an increase in mitotic activity. We suggest that in the presence of an inflammatory background, and crucially in the absence of architectural complexity, it is safer to regard the changes as atypia or indefinite for dysplasia rather than low-grade dysplasia. From the practical point of view, it was often the case that a diagnosis of dysplasia triggers a surgical plan for colectomy. The difficulty lies in distinguishing between absent for dysplasia due to three factors: small unrepresentative biopsies; badly orientated specimens; or reflection for a lack of confidence by the reporting pathologists. We strongly recommend sticking to strict, well-laid out histopathological criteria. Despite the approved criteria, Dixon et al.\cite{2} reported a disturbingly significant interobserver variation on high grade dysplasia. Due to the huge clinical significance of such a diagnosis, they suggested that such biopsies need to be reported by two pathologists, with one of them having a special interest in such lesions.\cite{2} Such a practice has become routine in UK. In our referral practice or during the Multi-Disciplinary Team Meetings (Tumour Board), we have downgraded diagnoses of low-grade dysplasia reported by general pathologist without support from GI pathologist. We have also seen colectomies based on experience. Features of reactive atypia include enlarged and stratified nuclei, along with an increase in mitotic activity. We suggest that in the presence of an inflammatory background, and crucially in the absence of architectural complexity, it is safer to regard the changes as atypia or indefinite for dysplasia rather than low-grade dysplasia. From the practical point of view, it was often the case that a diagnosis of dysplasia triggers a surgical plan for colectomy. The experiences of many centres showed that negative colectomies can be avoided.\cite{3}

### Acute phase radiation and ischemia

Acute phase radiation and ischemia are two important entities reported to produce enough significant epithelial changes that can be easily mistaken for colonic dysplasia. Mucosal changes in acute phase radiation bowel disease are commonly seen in specimens after short course radiotherapy for pelvic cancer. The histological features of the benign epithelial cells in the radiation field are so atypical that they mimic high-grade dysplasia (Fig. 1).\cite{4} The presence of significant eosinophilic infiltrate, commonly with eosinophilic abscesses, gives way to such a diagnosis. It is, however, essential to have a clinical history to avoid this pitfall.

Ischemic colitis has been reported to create a morphological picture mimicking dysplasia. Zhang et al.\cite{5} described a series of ischemic colitis in which in 8 out of 28 cases, the epithelial changes resembling dysplasia were labelled as pseudo dysplasia. These changes comprise irregular gland architecture, high nuclear cytoplasmic ratio and pseudo-stratification of epithelial cells within the crypts. True dysplasia shows, in addition, atypical mitoses together with glandular budnings and back-to-back glands with little or no stroma in between. The study suggested that, as in many cases of ischemic colitis, changes might show features resembling IBD including atypia of epithelial cells. These atypical reactive ischemic changes could be misinterpreted as true dysplasia complicating inflammatory bowel disease leading to mismanagement of such patients. Abraham et al.\cite{6} employed immunohistochemistry (IHC) in an attempt to delineate true dysplasia from pseudo dysplasia in ischemic colitides. They looked at 99 resections of ischemic colitis and found pseudo dysplasia in 15 specimens. When they compared pseudo dysplasia with genuine dysplasia complicating IBD, they found no difference in IHC staining patterns of P16, P53, and MIB-1 between the two entities. The study concluded that distinction requires recognizing the clinical context rather than relying on IHC. Helpful histological features in ischemic colitis include congestion, haemosiderin deposition, and fibrosis of the submucosa.

### Adenomatous polyps

Adenomas are the most common dysplastic lesions and prime precursors of carcinoma in the colon and rectum. Removal of adenomas reduces the risk of cancer.\cite{7}

There are various techniques of removing polyps ranging from cold or hot snare and forceps, endoscopic mucosal resection, and endoscopic submucosal dissection. The aim is to remove the entire polyp - preferably in one piece and with clear margins – for the pathologist to accurately assess the biological behaviour. The recurrence rate of be-
nign polyps is between 13.8% within 1 year and 60% within 3 years.\[5\] If the clinician decides to biopsy the lesion, there is the potential of underdiagnosis. One study on neoplastic polyps showed that whilst biopsy was accurate in differentiating neoplastic from non-neoplastic lesions, it was inefficient in ruling out malignancies in all cases.\[9\] In biopsying malignant polyps, the same study showed false negative reporting in 18.5% of cases when compared with the definitive surgery, where the entire specimen became available.\[9\] For this reason, the authors suggested that in cases where the adenomatous tumour shows no histopathological features of complete removal and does not contain an invasive element, the report should be presented in the following way: “This is a (identify tubular, tubulovillous or villous) tumour showing (low or high grade) dysplasia and no evidence of malignant transformation. If this is representative of the lesion, then this is an adenoma. If, however, it is part of a larger lesion then a more sinister pathology cannot be excluded”.

The histological features of complete removal are the presence of normal colonic epithelium on both sides of the tumorous element and in some techniques hyalinised amorphous material at the base of the specimen.\[10,11\] The above reporting style enables the pathologist to be more accurate in passing important information to the clinician and ultimately to the patient. This work was subsequently confirmed in a more comprehensive study in 2014 where false positive reporting was found in 18.8% of cases when the tumour biopsies were compared to the definitive resection surgery.\[12\] Furthermore, in this study, approximately 50% of the polyps that were initially reported by the pathologists as adenomas were in fact stages T2 and T3 malignancies. We suggest the reason for the false negative initial reporting is due to poor biopsy representation which might be due to either superficial biopsy with no invasive element included, or the biopsy being taken from the benign part of a polyp which had undergone partial malignant transformation (Fig. 2).

**Pseudo-invasion**

Pseudo-invasion is classically encountered in solitary or multiple Peutz-Jeghers (P-J) polyps. This type of pseudo-invasion is regular, almost symmetrical in terms of the growth of epithelial crypts into the submucosa and is associated with muscular proliferation resembling the characteristic appearance of a tree branch-like structure.\[13\] It is important to note that malignancy can complicate P-J polyps thus making the diagnosis even more challenging. The other important and more common condition of pseudo-invasion is basically encountered in the pedunculated polyp. This type of morphological feature is seen more often in the sigmoid colon when there is mucosal herniation into the submucosa, probably due to faecal stream pressure. Thus, applying strict histopathological criteria and taking full consideration of the clinical situation is important before making a diagnosis of invasion.\[14\] When comparing misplaced glands, prolapsed benign, or adenomatous crypts with invasive adenocarcinoma, the latter usually shows cytomorphological features of high-grade dysplasia along with desmoplastic reaction, which is by far considered the most important feature of malignancy. The crypts in pseudo invasion still retain their ‘cuff’ of normal lamina propria, which is not the case in true invasion (Fig. 3). The other features of pseudo-invasion are a lack of desmoplasia, the retention of the same degree of cellular atypia as the surface epithelial element, containing foci of hemosiderin pigmentation.

[Yantiss et al.\[15\]] have reported increased staining of the submucosal epithelium for matrix metalloproteinase 1 (MMP-1) and/or p53, combined with decreased staining of the submucosal epithelium for membranous E-cadherin, for establishing a diagnosis of adenocarcinoma. It is worthwhile validating this study as the degree of confusion in reporting pseudo invasion has come to light as a significant problem during the National Screening Programme for polyps in the UK. Following the start of this programme,

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**Figure 2.** Benign part of a polyp which had undergone partial malignant transformation.

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**Figure 3.** The crypts in pseudo invasion still retain their ‘cuff’ of normal lamina propria which is not the case in true invasion.
there was growing demand to create a board of experts to look at the ‘difficult’ polyps. In one publication from the board, 69% of the cases which originally were diagnosed as malignant polyps were subsequently downgraded by the experts to benign and the diagnoses were replaced by pseudo-invasion.[16] The authors suggested that such difficult polyps should be reported by two pathologists to minimise the chance of errors. In fact, double reporting of cancer or suspected cancer has become routinely practiced in UK.

**Assessment of muscularis mucosa in invasive carcinoma**

The muscularis mucosa (MM) is a crucial landmark in assessing invasion in colorectal cancer. Invasion beyond the MM heralds the potential dissemination of the disease by blood, lymphatics, or local extension. Often the biopsy shows invasion beyond the remnant of architecturally disturbed MM into the submucosa, but on occasion the MM is not available for inspection as it is destroyed by the malignant cells. The work of Jeziorska et al.[17] showed conclusively that cancer cells produce gelatinase B (MMP-9) which digests the MM facilitating the progression of the malignant tissue to invade the subjacent tissues (Fig. 4). This phenomenon creates a practical anomaly. On one hand, the classic teaching is to diagnose malignancy when invasion through the MM is established but on the other hand, the biopsy may not include the destroyed MM. The pathologist must then rely on other parameters to make a diagnosis of invasion. In one study, when an experienced pathologist looked blindly at mucosal biopsies of tumours in which the MM was not represented in the sections and applied strict criteria - namely desmoplasia, intraluminal necrosis, high grade, dysplasia presence of ulceration, irregularly infiltrating glands, and lympho-vascular invasion - the correct diagnosis was arrived in 41 out of 42 cases when compared to the specimen received subsequently from the definitive surgery.[18] Caution must be applied as desmoplasia can be seen in adenomas after been biopsied.[19] It is advisable that in an unrepresentative, often superficial, biopsy of a neoplastic polyyp, even after applying all possible recognised histopathological parameters of malignancy without coming to any conclusion, it is in these circumstances that imaging in the hands of the experts comes to the assistance as in such cases it demonstrates if there is invasion and may accurately assess the stage.[19]

**Lymphovascular invasion (LVI)**

It has been customary to bundle lymphatic channel (LI) and blood vessel invasion (VI) into one prognostic parameter as lymphovascular invasion (LVI) (Fig. 5). This has created a significant therapeutic confusion as there is a clinical and academic need to separately assess the risk of LI and VI. These should be regarded as two different entities and to each there is a different anatomical destination. In general the natural destination of LI is to the lymph nodes while the destination of vascular invasion is to the portal vein, then the liver, lung, and other organs. We have argued strongly that a distinction between the two parameters must be established in the histopathology report by applying immunohistochemical markers like podoplanin which stains lymphatic channels as a marker of LI and CD34 which stains the blood vessel channels as a marker of VI. This is important as each invasive modality has a different outcome and may require different treatment in the sense that vascular invasion may require additional chemotherapy.[20] The latest edition of the minimum data set for reporting CRC in the UK has catered for such a suggestion thus putting the responsibility on the pathologists to undertake this important task.

*Figure 4.* Cancer cells produce gelatinase B [stained by matrix metalloproteinase (MMP)-9] which digests the muscularis mucosa (MM) facilitating the progression of the malignant tissue to invade the subjacent tissues. The figure in the left highlights positive staining of MMP-9.
Observer variation in staging T1 CRC

There are many staging systems for early cancer (T1) including malignant polyp. Chronologically, the various staging systems appeared in the literature in this sequence: Haggitt 1985, Kudo 1993, Kikuchi 1995, Kitajima 2004, and Ueno 2004.[21-25] Most widely, the stages used in the Western World are Haggitt for pedunculated and Kikuchi for sessile polyps. Although these classifications/staging systems are useful in planning management and predicting outcome, they suffer from a few practical problems. Quirke et al.[26] drew the attention to the technical limitations like fragmentation of specimen and absence of muscularis propria (MP) that may lead to misinterpretation and interobserver variation. The presence of MP is essential in giving Kikuchi classification. Absence of MP invalidates Kikuchi staging. Quirke identified the frustrating situation of specimen fragmentation when it becomes impossible to accurately assess the depth of invasion and often failure to identify the completeness of excision. Disturbingly, the work from Davenport et al.[27] showed that there is significant interobserver variation amongst experienced gastrointestinal pathologists when assessing 56 colorectal malignant polyps even when using agreed prognostic parameters like width of invasion and LVI.

In Davenport et al.[27], the inter observer variation for depth of invasion was 0.71 (good) and for width of invasion was 0.48 (moderate). In our study, only fair agreement (kappa = 0.35) was achieved in the assessment of this parameter as reporting vascular invasion amongst pathologists suffers interobserver variability with only low to moderate agreement in the literature.

There has been confusion between the Kudo and Kikuchi’s classification ever since the first paper of Kudo was published addressing the staging of T1 invasion into the submucosa. Although there is some overlap, Kudo introduced the term of submucosal invasion (sm). He divided the submucosa into three parts, grading the invasion to the submucosa as sm1, sm2, or sm3. This classification includes the width of the invasion. Kikuchi’s classification is slightly different as it grades the sm1 if the tumour extends to slight submucosal invasion from the muscularis mucosa to the depth of 200 to 300 µm, sm3 stands for carcinoma invasion reaching near, but not involving, the inner surface of muscularis propria, while sm2 symbolises intermediate invasion between sm1 and sm3. Unfortunately, many pathologists, in the absence of MP, started wrongly equating the depth of invasion with millimetres (mm). For example, they erroneously equate sm1 to 1 mm, sm2 to 2 mm, and sm3 to 3 mm. We have shown that the depth of submucosa varies significantly between individuals and even within different areas of the submucosa in the same individual.[28]

This means that if the depth of the submucosa is 5 mm and the depth of invasion is 3 mm, it is wrong to give it a sm3 grade. Similarly, if the depth of the submucosa is only 1 mm and the invasion is 1 mm, it is wrong to equate the stage as sm1. We also suggested giving the depth in millimetres, and if the MP is present, we add Kikuchi. Failing that, we have to indicate the degree of invasion by millimetres only. We think that for the various staging systems to be of value the pathologists should endeavour to apply the strictest criteria of the system used in the assessment of such lesions. Any personal modification invalidates the clinical value of the system. We feel that by applying ‘personal modifications’ of any classifications will give wrong outcome data, which makes it impossible to intercalate in a unified way.

Pseudo-sarcoma and stromal proliferation

There are cases in which there is atypical stromal proliferation that could mimic sarcomas. These lesions can create significant problems to the inexperienced pathologist, thus leading to unnecessary radical surgery for a completely benign condition. Giovanni et al.[29] described lesions like inflammatory fibroid polyt (IFP), fibroelastic polyt (FP) and inflammatory myofibroblastic tumours (IMT) as examples of these phenomena. Each of these lesions has fairly distinct microscopic features and IHC stains differentiating one entity from the other. Macroscopically, IFP presents as a submucosal polypoidal mass covered by either intact or ulcerated mucosa. Macroscopically, there is bland proliferation of spindle and stellate mononuclear cells intermixed with eosinophils and plasma cells. Sometimes multinucleated cells and myxoid stroma can be seen focally. Sarcomas have more aggressive looking stromal components with high mitotic rates, focal areas of necrosis with tendency to infiltrate surrounding tissues and vessels.

Immunohistochemical stains show strong positivity for CD34 in the spindle cells especially around blood vessels. IMT, on the other hand, is a myofibroblastic proliferation with dense plasma cells infiltrate and strong positivity for actin. It is important to make a distinction between IFP,
which always runs a benign course, and IMT, which can recur locally. FP is characterised by proliferation of vimentin positive bland spindle cells showing low proliferative activity separating the crypts of the lamina propria with variable amount of chronic inflammatory infiltrate (Fig. 6). Shekitka and Helwig [30] reported a cohort of lesions of what they called ‘deceptive bizarre stromal cells’ in polyps and ulcers that need to be recognised to avert over interpretation. They described 22 colonic lesions of which 18 appeared as polyps and 4 as ulcers, all containing atypical stromal proliferation. Those lesions were seen sporadically or in patients with IBD. Misinterpretation of such lesions may result in major resection for benign pathology. These lesions can be single or multiple. Microscopically, sections can show bizarre atypical cells close to ulcer or regenerated mucosa with inflammatory cell infiltrate. These cells are thought to be reactive mesenchymal cells. Mitosis is not common in these cells and, if seen, is never atypical. If high mitotic figures are noted or any atypical mitosis is present, the diagnosis should be reconsidered. IHC of the bizarre cells show vimentin positivity while negative for desmin, SMA, S100, CEA, and EMA.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Author contributions

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Pitfalls in Reporting Neoplastic Colon Biopsy


Трудности при установлении неопластических и псевдо неопластических поражений толстой и прямой кишки

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Резюме

Введение: Биопсия толстой кишки составляет большую часть ежедневной работы патологоанатомов. В пределах различных патологических образований существуют гистологические диапазоны и вариации. Неосведомлённость обо всех этих вариациях может привести к неправильной диагностике неопытным патологоанатомом и, соответственно, к неправильному лечению.

Цель: Цель этой статьи состояла в том, чтобы обратить внимание патологоанатома на некоторые наиболее распространённые и/или важные трудности при рассмотрении диагноза опухолевых состояний толстой кишки.

Материалы и методы: Мы выделили основные неопластические трудности в гистопатологических исследованиях биопсии толстой кишки.

Результаты: Согласно нашему опыту, трудности, описанные в этой статье, являются наиболее распространёнными проблемами, с которыми мы сталкивались. Таким образом, настоятельно рекомендуется двойная отчётность по сложным случаям, чтобы избежать проблем при сообщении таких случаев.

Заключение: Патологоанатом должен быть очень аккуратным, сообщая о некоторых наиболее распространённых проблемных случаях.

Ключевые слова

биопсия толстой кишки, гистопатология, новообразование, трудности