The pathology of colorectal polyps and cancers (including biopsy)

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Abstract

An understanding of the pathology of colorectal polyps and cancers is necessary in order to deliver the most appropriate therapy and devise effective screening programmes that reduce morbidity and mortality. We discuss the classification of polyps occurring in the colon and rectum, focussing on morphology and molecular pathology, with particular reference to the adenoma-carcinoma sequence and the serrated pathway of colorectal neoplasia. Knowledge of the normal structure of the large bowel is important to understanding the pathogenesis of colorectal polyps and the staging systems that are required for determining prognosis and therapy in colorectal cancer.

Keywords Adenoma; carcinoma; colon; endoscopy; histopathology; NHS Bowel Cancer Screening Programme; polyp

Introduction

Colorectal cancer (CRC) is one of the most commonly diagnosed malignancies in the UK, ranking third in frequency in both men and women,[1] and is the second most common cause of cancer death.[2] The majority of CRCs are believed to arise within adenomas, which are a common type of polyp. This review aims to outline the normal histology of the gastrointestinal tract and the pathology of colorectal polyps and CRC. We include a summary of the molecular pathology of CRC and discuss the staging systems that play a fundamental role in patient management.

Normal histology of the gastrointestinal tract

Histologically, the gastrointestinal tract consists of four concentric layers as one progresses outward from the lumen: the innermost *mucosa*, the *submucosa*, the *muscularis propria* and the outermost *serosa* or *adventitia*.

1. The *mucosa* consists of an epithelial lining, a supporting lamina propria that contains loose connective tissue rich in lymphocytes and plasma cells, and a thin smooth muscle layer, the muscularis mucosae, which separates the lamina propria from the submucosa. The epithelium comprises a single layer of columnar cells lining millions of regularly spaced crypts that span the depth of the lamina propria. The columnar epithelium hosts a variety of cell types such as goblet cells, absorptive colonocytes and endocrine cells. The crypts are aligned perpendicular to and extend to the muscularis mucosae, imparting a 'rack of test tubes' appearance (Figure 1). This arrangement increases the mucosal surface area for the purposes of absorption.
2. The *submucosa* lies external to the mucosa, is a more densely collagenous, less cellular layer than the mucosa and consists of major blood vessels, lymphatics and cells of the enteric nervous system.
3. The *muscularis propria*, a thick muscular layer that should not to be confused with the thinner muscularis mucosae, consists of an inner circular smooth muscle layer bounded by an outer longitudinal layer that forms the basis of peristaltic contraction. The muscularis propria also harbours cells of the enteric nervous system as well as many blood vessels and lymphatics.
4. The *adventitia* consists of loose connective tissue, containing fat, collagen and elastic tissues. When covered by a mesothelial cell lining, it is referred to as the *serosa*.

Classical adenomas

Classical adenomas are the precursor lesions for most CRCs. Endoscopically, adenomas may be polypoid or non-polypoid (i.e. flat or depressed). While polypoid adenomas are readily seen on colonoscopy, non-polypoid adenomas appear as small, flat-like mucosal discolourations and detection rates are lower. Such lesions should be designated using the Paris classification.[3] It has been proposed that there is an increased risk of CRC associated with flat or depressed adenomas,[4] although wider recognition and standardized reporting of these lesions is needed to confirm their clinical and pathological significance.

Histologically, an *adenoma* is defined as a proliferation of glandular epithelium with at least low-grade dysplasia. Current reporting guidelines recommend a two-tier classification of dysplasia into 'low' and 'high' grade,[5] which aims to improve diagnostic reproducibility, thus ensuring comparability of data between centres. *Low-grade dysplasia* in the colonic mucosa is manifested by cytological atypia, whereas a diagnosis of *high-grade dysplasia* is usually based on architectural changes in addition.

The most common type is the *tubular adenoma*, which has a smooth surface and parallel crypts, similar to normal epithelium. A *villous adenoma* is covered in finger-like projections that consist of long thin delicate fibrovascular cores that show little branching and are covered by at least low-grade dysplastic epithelium (Figure 2). A *tubulovillous adenoma* has features of both. At least 20% of an adenoma should be villous to allow classification as tubulovillous adenoma, and 80% villous to allow classification as villous adenoma.[6] The associated risk of malignancy for adenomas is highly correlated with increasing size, villous architecture and the presence of high-grade dysplasia. Subsequent surveillance colonoscopies should be performed yearly, 3-yearly or 5-yearly according to risk-stratification based on the size and number of adenomas.

Familial adenomatous polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder characterized by the development of hundreds of

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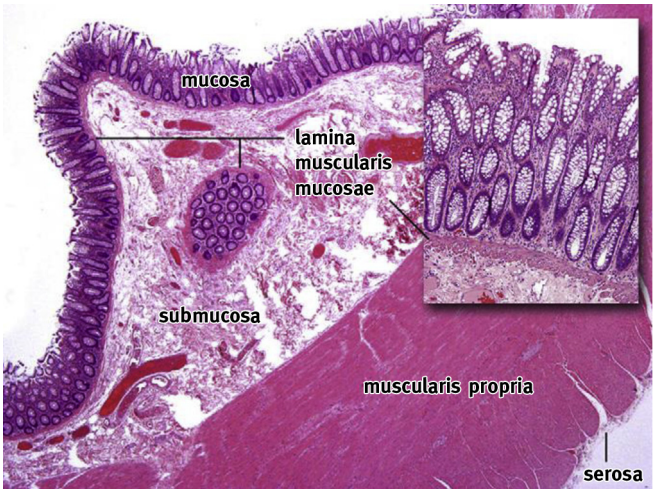

Figure 1 Normal histology of the colonic wall. The muscularis mucosae separates the mucosa from the submucosa. Inset: Normal mucosal crypt architecture.

adenomas in the colon and rectum during the second decade of life. These polyps are morphologically indistinguishable from sporadic adenomas. Disease prevalence in the UK is estimated at 1 in 18,976, with an incidence of 1 in 8619.[7] FAP is caused by germline mutations in the *adenomatous polyposis coli (APC)* gene at chromosome 5q21. Diagnosis is based on a suggestive family history, and clinical and endoscopic findings. Whenever possible, the clinical diagnosis should be confirmed by genetic testing. When the *APC* mutation in the family has been identified, genetic testing of all first-degree relatives should be performed. Individuals with FAP carry a 100% risk of CRC, which generally develops a decade after the appearance of the polyps. Consequently, prophylactic colectomy is the standard therapy for individuals carrying *APC* mutations. Adenomas may also develop adjacent to the ampulla of Vater and in the stomach. Moreover, FAP is associated with extraintestinal manifestations such as *congenital hypertrophy of the retinal pigment epithelium* (CHRPE). Variants of FAP include *Gardner syndrome* and *Turcot syndrome*. In addition to intestinal polyps, patients with Gardner syndrome can have osteomas of the mandible, skull, and long bones, epidermal cysts, desmoid tumours, thyroid tumours, and dental abnormalities, including unerupted and supernumerary teeth. Turcot syndrome is rarer and is characterized by intestinal adenomas and tumours of the central nervous system. Some FAP patients without *APC* loss have mutations of the base-excision repair gene, *MUTYH*. Certain *APC* and *MUTYH* mutations are associated with attenuated forms of FAP, which are characterized by fewer colorectal adenomatous polyps and the delayed appearance of CRC.[8]

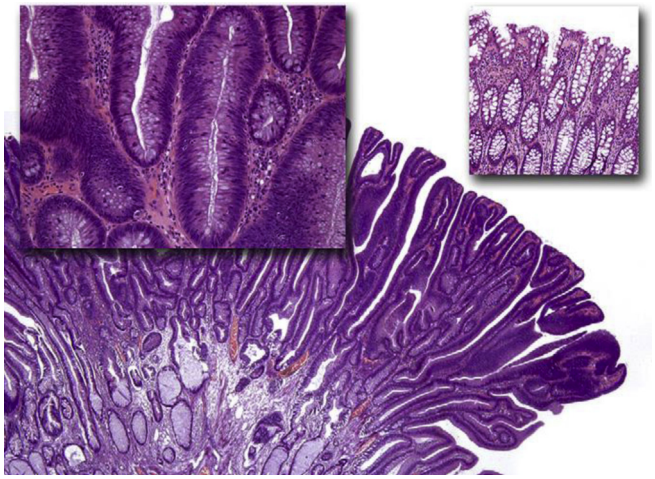

Figure 2 Villous adenoma. Inset (left): Low-grade dysplasia. Inset (right): Normal mucosa for comparison.

Serrated lesions

The 'serrated spectrum' is a heterogeneous group of lesions that include *hyperplastic polyps* (HPs), non-dysplastic *sessile serrated lesions* (SSLs), dysplastic *traditional serrated adenomas* (TSAs), and mixed polyps with both hyperplastic and adenomatous components.[9] Serration is a histological term referring to saw-toothed glandular architecture. Unlike classical adenomas, serrated lesions are often sessile (i.e. flat and occupying a broad base) making endoscopic detection more difficult.

The hyperplastic polyp (HP) is the most commonly encountered lesion in patients undergoing bowel cancer screening. These tend to occur in the distal colon and rectum and are often small in size (<5 mm). Typical HPs require no follow up after excision. Rarely, patients present with numerous hyperplastic polyps as part of the hyperplastic polyposis syndrome.

The term 'sessile serrated lesion' (SSL) has been applied to polyps that are usually between 5 and 10 mm in size and display complex architectural abnormalities with minor cytological atypia. SSLs are usually found in the proximal colon and are more common in women. The risk of malignant transformation is highly variable. Consequently, the optimal frequency of follow-up is debated and recommendations vary between 1 and 3 years.

The traditional serrated adenoma (TSAs) is by definition dysplastic and a recognized precursor for serrated adenocarcinoma. The majority are found in the distal colon, tend to be larger than other serrated lesions (>10 mm) and are often pedunculated (i.e. they have a stalk or pedicle). In view of their higher risk of malignant transformation, surveillance screening for TSAs and mixed polyps with neoplasia should comply with that for classical adenomas.

Inflammatory polyps

Inflammatory polyps form as a result of repeated cycles of injury and healing, and are usually seen as a complication of chronic *inflammatory bowel disease* (IBD), particularly *ulcerative colitis* (UC). Isolated islands of regenerating mucosa protrude into the lumen, thus appearing polypoid. Occasionally, they may harbour foci of dysplasia, especially in the context of UC (discussed below). Inflammatory polyps are also seen in association with diverticulosis and mucosal prolapse. Furthermore, sporadic, single inflammatory polyps can occur.

Dysplasia-associated lesion or mass in inflammatory bowel disease

It is widely accepted that chronic IBD increases the risk of CRC, particularly in patients with UC who have had episodes of severe pancolitis over many years. Dysplasia in UC may be classified as

