Pathology of colorectal neoplasia

Frank Carey

Abstract

Colorectal adenomas and cancers are common. Diagnosis and management of these lesions requires close clinicopathological correlation. This article emphasizes clinically important issues in management of adenomas, including serrated lesions, and early stage cancers removed by local excision. Pathological interpretation and staging of formal resection specimens is also discussed. The biology of colorectal cancer is emphasized, particularly reflecting the need for molecular analysis to guide adjuvant oncological treatment.

Keywords Cancer biology; colorectal adenoma; colorectal carcinoma; polyp cancer; serrated polyp

Introduction

Colorectal cancer (CRC) is a significant public health and surgical management issue. CRC is the third commonest visceral malignancy in both sexes and is the second commonest cause of cancer death in the UK and other western countries. Surgical resection is still the mainstay of treatment in this disease and pathological examination of the resected cancer is the key to determining prognosis and guiding adjuvant oncological therapy.

Most CRC develop from adenomatous polyps. Identification, removal and pathological diagnosis of polyps is an important part of endoscopy practice. Detection of adenomas and other colorectal polyps has increased markedly with the introduction of bowel cancer screening programmes.

The present review will outline the main pathological issues of clinical importance in colorectal endoscopic and surgical practice. Different pathological and molecular pathways to cancer will be briefly outlined, an increasingly important factor in modern CRC oncology.

Colorectal adenomas and other polyps

A polyp is simply an abnormal protrusion from a mucosal surface. Adenomas are benign neoplasms of the large bowel mucosa. Seldom symptomatic, the main importance of adenomas is that they are the precursor lesion for the great majority of colorectal cancers. Adenomas increase in incidence with age. Multiple lesions, particularly in younger individuals, raise a suspicion of an inherited polyposis syndrome, most commonly familial adenomatous polyposis (FAP). In this condition there is an inherited mutation of the adenomatous polyposis coli (APC) gene. Patients with this condition also have an increased incidence of other neoplasms including particularly adenomas and cancers of the ampulla of Vater and desmoids tumours (locally aggressive fibromatosis of the abdominal wall and/or mesentery).

The presence of adenomas is a marker of cancer risk. This risk becomes clinically significant and justifying endoscopic surveillance with larger (<10 mm) adenomas and when three or more lesions of any size are present. Microscopic identification of high-grade dysplasia is also a risk marker in many series (Figure 1).

There is extensive epidemiological and molecular evidence linking adenomas to development of cancer. The earliest detectable form of colorectal cancer (so-called polyp cancer) is seen as a focus of invasive cancer detected by the pathologist in a polypectomy specimen removed at endoscopy as a presumed benign adenoma (Figure 2). This was formerly an unusual finding but polyp cancer has become relatively common following the introduction of population screening. These cases provide particular challenges. In the first instance microscopic diagnosis of polyp cancer is often difficult since pedunculated polyps often show displacement of mucosa into the stalk as an artefact of trauma in peristalsis. Management of patients with confirmed polyp cancer is also problematical. The great majority of these have an excellent prognosis and are cured by the endoscopic procedure. Some need to proceed to formal surgical excision of the affected segment of bowel. These higher risk individuals are identified by microscopic evidence in the polypectomy specimen of poorly differentiated invasive malignancy, margin involvement by cancerous tissue, or of vascular and/or lymphatic invasion by tumour. It is likely that management criteria will be modified over time by evidence emerging through follow-up of screen detected cases.

Serrated neoplasms of the colorectum

In recent years there has been considerable interest in the biology and clinical manifestations of a range of epithelial polyps and cancers characterized by epithelial serration. This is defined by the microscopic finding of a characteristic 'saw-tooth' outline to the epithelial surface (Figure 3). The most common lesion in this category is the hyperplastic (also known as metaplastic) polyp, a very common dome shaped polyp seldom more than 5–6 mm in dimension and found mainly in the rectum and sigmoid colon. These lesions have no evidence of true epithelial dysplasia and an extremely low risk of progression to cancer. Serrated adenomas are larger lesions with epithelial serration and cytological dysplasia. These are considered equivalent in risk to similar sized conventional adenomas.

Much attention has of late been focussed on a curious serrated polyp most often seen in the right colon – the sessile serrated lesion (known in the USA as sessile serrated adenoma). This flat lesion is easily missed at conventional colonoscopy but is seen better with narrow band imaging. It is characterized by serrated epithelial morphology without conventional dysplasia but with characteristic architectural features of dilated misshapen crypts (Figure 3). Though the clinical outcome of these lesions is not certain current practice is to treat them as equivalent to adenomas of similar size.

Biology of colorectal adenoma and carcinoma

There are several distinct molecular pathways to cancer in the large bowel and some of these have direct morphological

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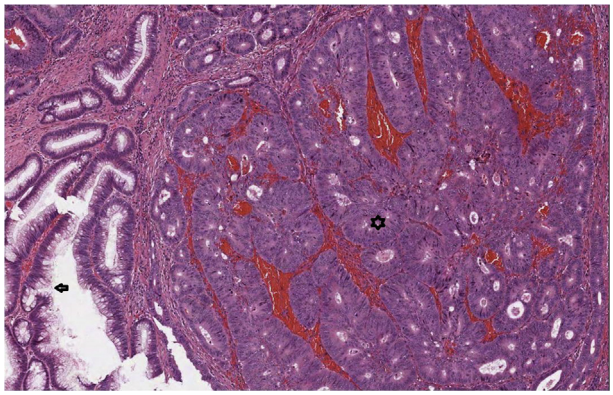

Figure 1 Adenoma showing area of low-grade dysplasia (arrow) with high-grade dysplasia (star) characterized by architectural crowding and increased level of nuclear morphological abnormality.

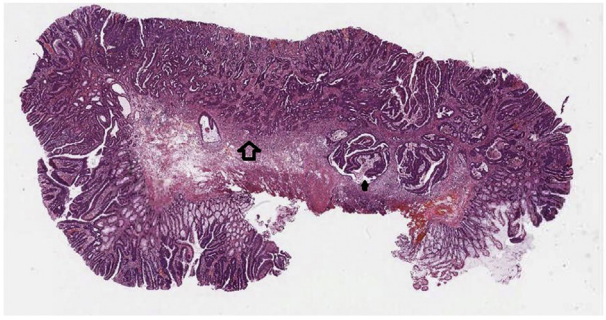

Figure 2 Endoscopically resected colorectal polyp. There is an adenoma with a focus of superficially invasive adenocarcinoma (open arrow) showing neoplastic epithelium infiltrating into a fibrous ('desmoplastic') stroma. The solid arrow shows a focus of traumatic epithelial misplacement of benign adenomatous glands. This can be mistaken for cancer.

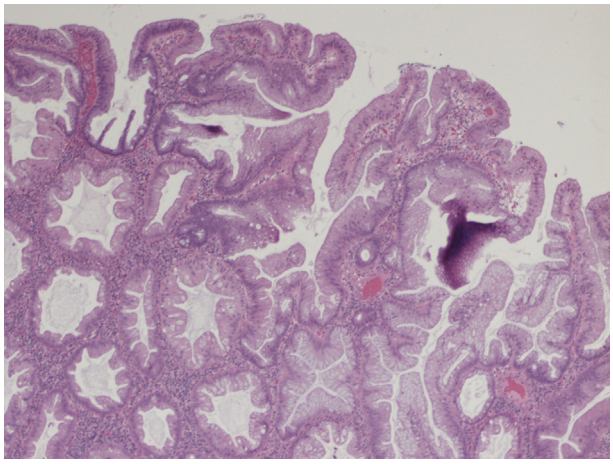

Figure 3 Microscopic image of sessile serrated lesion of right colon. The 'saw-toothed' surface outline of the epithelium is evident. The crypts are characteristically distorted and architecturally complex but there is none of the conventional cytological dysplasia seen in Figure 1.

correlates. Most colorectal cancers, especially in left colon and rectum, are characterized by aneuploidy (abnormality of chromosome number, the so-called chromosomal instability pathway). Most such tumours have mutations of the p53 gene and about half have K-ras mutations. K-ras (and its sister gene N-ras) mutation status is commonly tested clinically in patients with limited metastatic disease since treatment with EGFR pathway inhibitors such as cetuximab is not effective in patients with ras-mutated tumours.

Serrated polyps and the cancers arising from them tend to be right sided and to be stable in chromosome number. They do however have a pattern of genome wide mutation which can be detected by looking at changes in marker genes (microsatellite instability). This mutator phenotype can occur through an inherited abnormality of DNA mismatch repair genes (Lynch syndrome) or by acquired dysfunction of one of these genes (usually h-MLH1) by hypermethylation of its promoter sequences. Mutation of B-raf is also a feature of some cancers with the mutator phenotype. This latter abnormality has an adverse relation with patient prognosis.

Pathology of colorectal cancer

Understanding the pathology of colorectal cancer has been critical in developing current concepts of disease biology. Pathology is also crucial in management of the individual patient and it is this aspect that will form the main focus of the present discussion.

Unlike other major cancer sites such as the lung, the great majority of colorectal cancers are of a single histogenetic type (i.e. adenocarcinoma). The tumours arise ultimately from pluripotential stem cells present in the large bowel crypt. Occasionally other histological variants present as primary colorectal neoplasms, the second most frequent tumour type being neuroendocrine tumours of varying grades of aggression ranging from clinically effectively benign to high grade malignant. In managing neuroendocrine lesions it is important to avoid over-treatment, especially of low-grade endocrine (carcinoid) tumours of the rectum which tend to be extremely indolent.

Adenocarcinoma can be subdivided by its microscopic features into well, moderately and poorly differentiated forms. Poorly differentiated cancers often have a mucinous signet ring morphology and these cancers have a distinctly poorer prognosis than the generality of cases (Figure 4). Most patients will have a preoperative biopsy histological diagnosis. This is particularly important for rectal cancers since a significant proportion of these individuals will have neoadjuvant chemoradiotherapy prior to definitive surgical excision.

Surgical management of colorectal cancer has evolved markedly over the last couple of decades. Significant parts of this progress have involved close collaboration between specialist surgeons and pathologists. Particular emphasis has been placed on the importance of macroscopic assessment of the surgical resection specimen. Recording of the quality of mesorectal fascial excision by the pathologist is an important and routine part of surgical audit and has been instrumental in reducing local recurrence rates in rectal cancer. Management of the lowest rectal cancers by abdominoperineal excision has been another

