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Case report

Endophytic malignant transformation within flat adenoma of the colon: a potential diagnostic pitfall

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Abstract. A 74-year-old man was found to have a 1 cm, slightly elevated and flat, red mucosal lesion of the descending colon. An endoscopic biopsy showed a structure characteristic of a tubular adenoma. The surgical specimen revealed an inverted, transmural, solid and cystic lesion. The superficial (intra-mucosal) component of the neoplasm was histologically characteristic of a flat adenoma, showing epithelial dysplasia. However, the contiguous deep component was a well-differentiated adenocarcinoma extending to the serosa and demonstrating the unusual features of a circumscribed lobulated topography and the absence of an inflammatory/desmoplastic stromal reaction. Endophytic malignant transformation within a flat adenoma should be distinguished from conditions of misplaced glandular epithelium such as localized colitis cystica profunda. Complete and full mucosal thickness endoscopic snare removal is indicated in order to assess the degree of epithelial dysplasia and detect endophytic malignant transformation.

Key words: Flat adenoma – Flat carcinoma – Colon

Introduction

Flat adenoma of the colon is a recently recognized entity with a specific colonoscopic and histopathological appearance (Kuramoto et al. 1990; Muto et al. 1985; Wolber and Owen 1991). Although flat adenoma does not exceed 1 cm in radial diameter, it frequently exhibits high-grade epithelial dysplasia in contrast to polypoid adenomas of the same size (Wolber and Owen 1991). However, synchronous and contiguous invasive malignant transformation appears to be exceptional and only two such cases have been documented (Kuramoto and Oohara 1989) among flat mucosal lesions not exceeding 1 cm. In both cases, the invasive carcinomatous component did not penetrate beyond the submucosa. We report a 1 cm flat lesion of the colon whose entire mucosal aspect was characteristic of a flat tubular adenoma, whereas underlying contiguous and transmural malignant transformation was observed, without associated inflammatory/desmoplastic stromal changes.

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Materials and methods

The specimen was fixed in 10% buffered formaldehyde. Sections were stained with haematoxylin-eosin and selectively stained with Masson's trichrome, periodic acid-Schiff, Alcian blue at pH 2.5 and Mayer's mucicarmine. Immunocytochemical staining for AE1/AE3 cytokeratin (Boehringer Mannheim, Laval, Quebec; dilution 1/300) and chromogranin (Boehringer Mannheim; dilution 1/300) was performed with the streptavidin-biotin-peroxidase complex method. Staining for carcinoembryonic antigen (CEA) (Dakopatts, Mississauga, Ontario; dilution 1/300) was done with the avidin-biotin-peroxidase complex method.

Case report

A 74-year-old man presented with a history of melaena for 2 to 3 days one month earlier and a weight loss of 6 kg over the previous 6 weeks. There was no abdominal pain nor recent change in appetite. There was no history of previous colorectal surgery, familial adenomatous polyposis or irradiation. His mother had developed carcinoma of the colon at age 84 years.

Physical examination was within normal limits, including normal skin and buccal mucosa. Sigmoidoscopic examination to 12 cm was within normal limits. Stools were negative for occult blood. Laboratory values were normal, including a negative serum CEA. Chest radiography was negative. A barium enema revealed a 1.5 × 1.0 cm contour defect in the proximal descending colon suggestive of a small carcinoma. During colonoscopic examination a 1.0 cm plaque-like, mostly flat mucosal lesion was seen at the splenic flexure and biopsied. As the biopsy revealed a tubular adenomatous architecture with significant epithelial dysplasia and because of the uncertain significance of these findings in the present setting, a segmental resection was performed. The patient had no evidence of disease at 16-month follow-up.

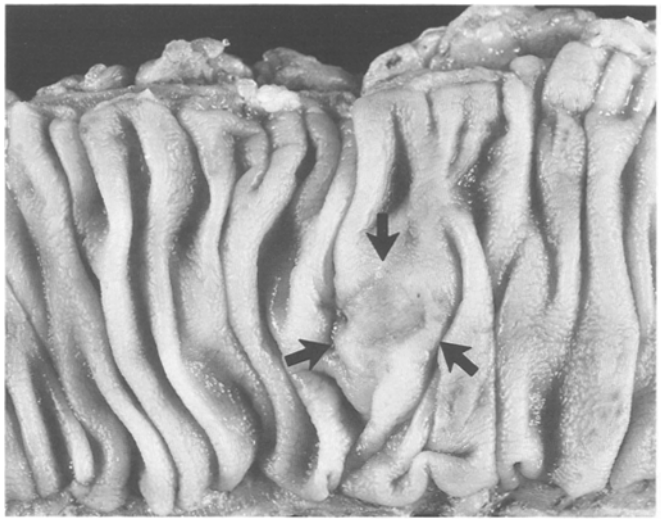

Fig. 1. Segment of colon showing a plaque-like, flat, non-ulcerated lesion (*between arrows*). Note the dull and finely granular surface

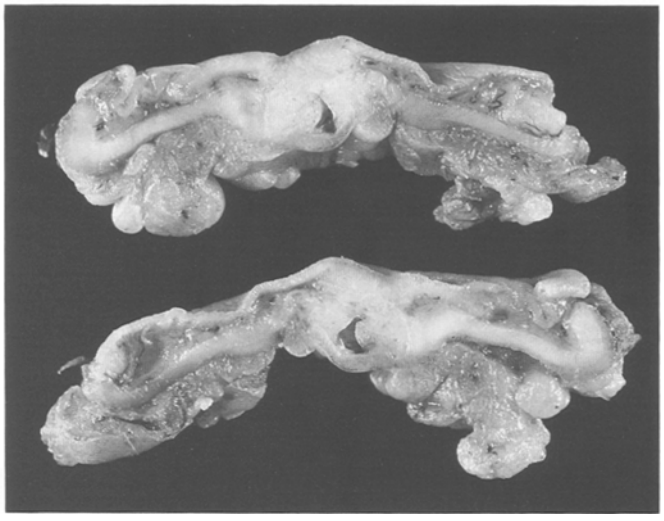

Fig. 2. Cross-section of bowel wall showing an inverted, solid white and partly cystic lesion extending to the serosal aspect

Fig. 3. Whole-mount view showing a lobular grouping of tubulocystic formations with transmural involvement of the colon in continuity with a flat adenomatous mucosal component

Pathological findings

Gross examination showed a 1.0 cm round, non-ulcerated and slightly elevated, mostly flat and focally depressed reddish mucosal lesion (Fig. 1). On cut surface the lesion was a $1.0 \times 0.8 \times 0.6$ cm circumscribed inverted tumour with transmural penetration. It was moderately firm, white and contained a few cavities of less than 2 mm filled with a clear straw-coloured fluid (Fig. 2).

Histological examination revealed a sharply demarcated lesion which was continuous from the luminal to the serosal aspect (Fig. 3). The intra-mucosal component (inner 1/4 of the total thickness) was characterized by tubules lined with a simple or pseudostratified columnar epithelium, and included a varying number of admixed mature and immature goblet cells (Figs. 3 and 4). A range of low to high-grade epithelial dysplasia was present, including the absence of cytoplasmic mucinous differentiation in high-grade zones (Fig. 4). Intervening lamina propria was present. The deep, contiguous component (outer 3/4 of the total thickness) revealed nodular aggregates of tubulocystic formations of varying size and shape, exhibiting a back-to-back positioning or a focal intervening delicate capillary framework (Fig. 3). The interface with the muscularis propria or the serosal surface was sharply demarcated. There was no associated inflammatory and/or desmoplastic stromal reaction. One discontinuous neoplastic gland surrounded by stroma

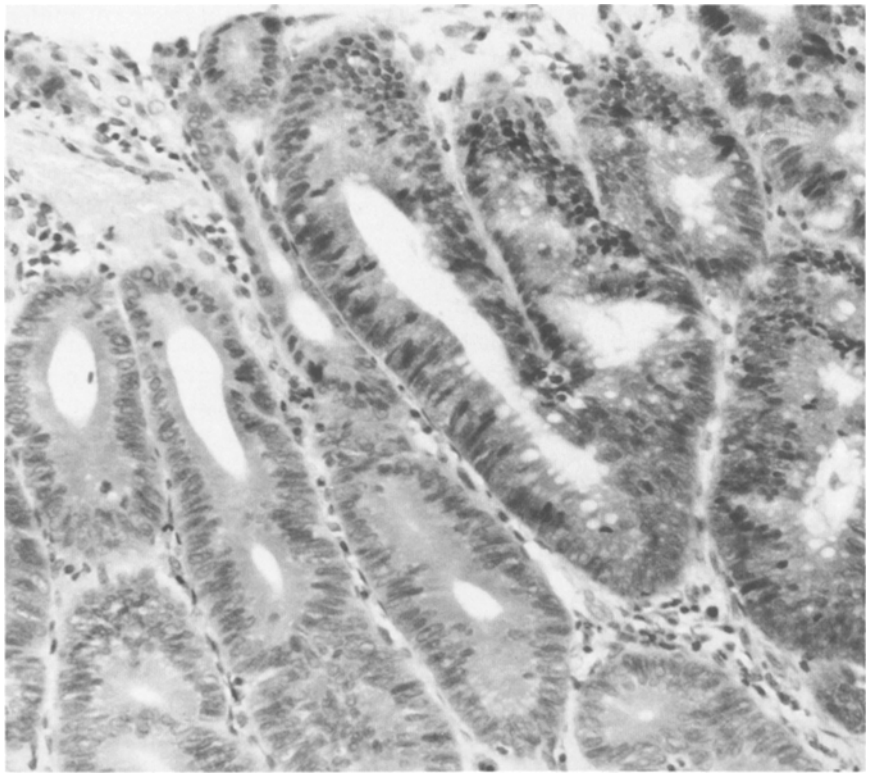

Fig. 4. Mucosal component showing a tubular cytoarchitecture with a full range of epithelial dysplasia, ×100

was seen in the pericolic fat. These tubulocystic formations were lined by a simple or stratified columnar epithelium, with nuclear hyperchromasia but without intracytoplasmic or luminal mucosubstance. Varying degrees of epithelial attenuation were present, including a flattened or non-discernable lining in dilated tubules or cysts. No mucus cyst or pool was found, whereas intraluminal cellular/nuclear debris were focally seen. Lymph node examination was negative for neoplasia.

A diffuse, moderate to marked cytoplasmic expression of cytokeratin, enhancing the presence of a flattened or discontinuous cyst lining epithelium was observed. CEA was detected as a focal, mild to moderate cytoplasmic staining with linear apical enhancement in the superficial component, whereas a much more frequent and stronger cytoplasmic staining was observed in the deep component. In contrast, only a delicate apical linear pattern of staining was seen in the adjacent normal mucosa. Chromogranin was not detected within the neoplasm.

The material originally obtained by endoscopic biopsy was representative of the superficial tubular adenomatous component.

Discussion

Flat adenoma of the colon is an unusual and recently recognized form of adenoma, first described by Muto et al. in 1985. It appears grossly as a slightly elevated red mucosal lesion, not exceeding 1 cm in radial diameter, and occasionally showing a central depression. Characterized by a pure tubular architecture, flat adenomas exhibit a much higher prevalence (up to 10 fold) of high-grade epithelial dysplasia than polypoid tubular adenomas of the same size (Wolber and Owen 1991). In spite of this observation, there have been very few reports of contiguous, adenomatous and invasive carcinomatous components in flat colonic mucosal lesions not exceeding 1 cm and while association with a synchronous, non-contiguous flat invasive carcinoma has been reported in 2 cases (Wolber and Owen 1991), invasive malignant transformation within flat adenoma has not been documented previously. A high incidence of "intramucosal microcarcinoma" within a flat adenoma has been reported by Japanese authors (Adachi et al. 1991; Muto et al. 1985); however, this designation is equivalent and synonymously used for high-grade dysplasia/carcinoma-in-situ in our terminology. However, in reported cases of flat colonic carcinoma not exceeding 1 cm (22 cases, mostly from Japan), a residual contiguous non-polypoid adenomatous component has been observed in only 2 cases (Kuramoto and Oohara 1989). In these, in contrast to the present tumour, invasive carcinoma involved at least the mucosal aspect and was associated with stromal desmoplasia.

The observation of vertical neoplastic growth without stromal reaction in the present case is intriguing. Whether this phenomenon results from the recognized loose and attenuated nature of the muscularis mucosae in a flat adenoma (Adachi et al. 1991; Muto et al. 1985), and/or malignant growth along a transmural path of least resistance (so-called locus minoris resistentiae), and/or impaired host response is unclear.

The unusual topography and tubulocystic architec-

ture of our neoplasm is superficially reminiscent of misplaced epithelium (such as pseudocarcinomatous invasion or localized colitis cystica profunda), and could lead to misinterpretation. However, in spite of the absence of inflammatory/desmoplastic stromal changes, the following features were indicative of invasive malignancy: the transmural topography (including one neoplastic gland within pericolic fat), the complex and back-to-back tubulocystic architecture, the absence of cytoplasmic mucinous differentiation, and the pattern of CEA expression. In contrast, misplaced glands as in pseudocarcinomatous invasion are associated with haemosiderin deposition, are partly surrounded by lamina propria, and are usually associated with mucinous pools/cysts (Fenoglio-Preizer et al. 1990). Furthermore, misplaced adenomatous glands have been observed exclusively in lesions of polypoid configuration. In the latter setting, glandular misplacement likely results from herniation and migration of epithelium through the muscularis mucosae, induced by peristaltic forces and twisting of the stalk with secondary ulceration (Fenoglio-Preizer et al. 1990). This phenomenon is not applicable to a flat adenomatous lesion. Although misplaced glands have been observed within or throughout the muscularis propria in a few cases of localized colitis cystica profunda, these observations were mostly made in a setting of radiation injury-induced stricture (Baratz et al. 1978; Gardiner et al. 1984). Furthermore, localized colitis cystica profunda is characterized by a hyperplastic, often ulcerated rather than adenomatous mucosal pattern, whereas mucus-containing cysts/glands are at least partly lined by normal colonic epithelium (Fenoglio-Preizer et al. 1990).

Neoplastic flat lesions of the colon are best detected by careful colonoscopic examination in conjunction with repeated inflation and deflation. Flat adenomas or carcinomas tend to disappear during inflation, whereas they become more visible on deflation (Adachi et al. 1991; Kuramoto and Oohara 1989; Kuramoto et al. 1990; Muto et al. 1985). Although our lesion was apparent on barium enema, smaller lesions may not be detectable (Kuramoto and Oohara 1989). A mucosal lesion not exceeding 1 cm and colonoscopically suggestive of a flat adenoma should be removed in toto, including some submucosal tissue, in order to assess the degree of epithelial dysplasia and rule out carcinomatous transformation. Complete endoscopic snare resection of such lesions has been shown to be feasible without anticipated complication (Adachi et al. 1991). Endoscopic biopsy followed by cauterization is to be discouraged because high-grade epithelial dysplasia and/or endophytic malignant transformation may not be detected.

As a result of the widespread use of the fiberoptic colonoscope and the increased awareness of the endoscopist, more flat neoplastic mucosal lesions of the colon will be detected. Further studies on these lesions will likely provide a better understanding of their pathobiology, and might elucidate the potential but speculative relationship between flat adenomas and de novo flat carcinomas.

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