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K. Murray · D. E. Nurse · A. R. Mundy

Malignant change in enterocystoplasty: a histochemical assessment

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Abstract Increasing numbers of cases of malignant tumours occurring in enterocystoplasties are being reported. Material from five cases of adenocarcinoma arising in such patients were studied using standard mucin and carbohydrate lectin staining methods. Sections from the tumour and adjacent and distant mucosa were stained to determine the pattern of histochemical changes. The abnormal staining patterns seen suggest that the adenocarcinomata arising at the enterovesical anastomosis are of intestinal origin. A hypothesis is advanced to explain the pathogenesis of these tumours.

Key words Enterocystoplasty · Malignant tumour Adenocarcinoma

Smith and Hardy [12] described the first malignant tumour, a transitional cell carcinoma, in an ileocystoplasty in 1971. The first report of an adenocarcinoma in an intestinal segment used for bladder reconstruction followed in 1973 [7]. There have since been an increasing number of case reports of malignant change in enterocystoplasties [4–6, 15]. This study was designed to determine, using standard histochemical techniques, whether these tumours represent adenocarcinoma of the bowel or primary vesical adenocarcinoma arising in areas of intestinal metaplasia.

Materials and methods

Histopathological material was obtained, with the permission of the original authors, from five cases of cystoplasty adenocarcinoma previously reported in the *British Journal of Urology* [4–6, 15]. Unstained, paraffin-embedded sections were provided from all the tumours and wherever possible from the cystoplasty bowel segment and bladder clear of the tumour margins. Mounted sections were stained with haemotoxylin and eosin (H&E) for orientation. Mucin staining was performed with alcian blue-periodic acid Schiff (AB-PAS) for acid and neutral mucins and high-iron diamine-alcian blue (HIDAB) to differentiate acid sialo- and sulphomucins. Lectin staining was carried out using peanut agglutinin – horse radish peroxidase (PNA-HRP) for *N*-acetylgalactosamine/galactose and *Ulex europaeus* agglutinin – horse radish peroxidase (UEA-HRP) for fucose residues [3]. The staining pattern for these techniques of normal intestinal mucosa, premalignant – so-called transitional mucosa – and gut carcinoma was determined on the basis of the criteria suggested by Felipe (1987).

K. Murray · D. E. Nurse · A. R. Mundy (✉)
Department of Urology, Guy's Hospital, St. Thomas Street, London SE1 9RT, UK

Results

H&E staining confirmed the presence of an adenocarcinoma in four patients. In the fifth patient the material available was felt to represent a dysplastic rather than a neoplastic polyp. The variation of pathology within a polyp on different sections could however explain this apparent discrepancy as the tumour was originally reported as a very well differentiated carcinoma [4]. In addition one patient had a well-differentiated papillary transitional cell carcinoma, superficial to and histologically distinct from an infiltrating adenocarcinoma. The histochemical staining pattern in these patients is shown in Table 1.

The sections from the cystoplasty bowel distant from the tumours demonstrated staining characteristics of the parent orthotopic bowel. Bladder mucosa showed no significant expression of mucin secretion and in these patients there was no evidence of intestinal metaplasia. The tumours arising in ileocystoplasties exhibited a predominant sulphomucin pattern. The unequivocal adenocarcinoma arising in a colocystoplasty had a sialomucin pattern typical of a colonic carcinoma. All the adenocarcinomata stained heavily with both peanut and *Ulex* lectins. There was no staining for either mucin or carbohydrate lectins in the synchronous transitional carcinoma. The mucin and lectin staining patterns of the tumours are summarised in Table 2.

Table 1 Staining patterns and lectin binding sites in normal "transitional" and malignant colonic mucosa (after Filipe 1987). *uc*, upper crypt, *lc*, lower crypt, *ABPAS*, alcian blue – periodic acid Schiff, *HIDAB*, high-iron diamine alcian blue, *PNA-NRP*, peanut agglutinin – horse radish peroxidase, *UEA-HRP*, *Ulex europaeus*, agglutinin – horse radish peroxidase

Tissue		Stain			
		ABPAS	HIDAB	PNA-HRP	UEA-HRP
Normal	uc	Mixed	Sulphomucin	0	0/+
	lc	Mixed	Sialomucin	0	0/+
Transitional	uc	Acid	Sialomucin	++	0/++
	lc	Acid	Sialomucin	0/++	0/+
Carcinoma		0/acid	Sialomucin	0/+++	0/++

Table 2 Mucin staining and lectin binding in cystoplasty tumours (for key to abbreviations see Table 1)

Ref.	Stain			
	ABPAS	HIDAB	PNA-HRP	UEA-HRP
[15] (1)	Non-secretory tumor		+	+
(2)	Acid	Sulphomucin	+++	+++
[5]	Acid	Sulphomucin	++	++
[4]	Mixed	Mixed	0	0/+
[6]	Acid	Sialomucin	++	+

Discussion

The majority of reported cases of carcinoma arising in bladders augmented or substituted with bowel have been adenocarcinomata. There are a number of striking similarities between the cases in the literature; a long latent period of 15 or more years, a history of post-cystoplasty urinary infection, a tendency to occur at the junction of bowel and bladder mucosa and a very poor prognosis. The exception is the case described by Grainger [4], where the tumour would appear to have been present at the time of the original surgery.

Although these tumours show a predilection for arising at the enterovesical anastomosis and thus could represent a primary adenocarcinoma of either the bowel or bladder component of the cystoplasty, no previous attempt has been made to determine the tissue of origin of these tumours.

Primary adenocarcinoma of the bladder is rare, accounting for less than 2% of vesical primaries. It has been suggested that glandular metaplasia of the transitional cell epithelium may represent a premalignant condition that can progress to adenocarcinoma or, more rarely, transitional carcinoma [2, 11, 1]. As focal goblet cell metaplasia has been described in the bladder remnant in cystoplasty patients [9], this raises the possibility that these tumours are primary bladder neoplasms. The mucin-staining pattern in colonic adenocarcinoma has been described by Filipe [3] together with a "transitional" pattern in which there is a replacement of the normal sulphomucins in the upper two-thirds of the crypts with sialomucins. This change in mucopolysaccharide production may be progressive from completely normal to frankly malignant mucosa.

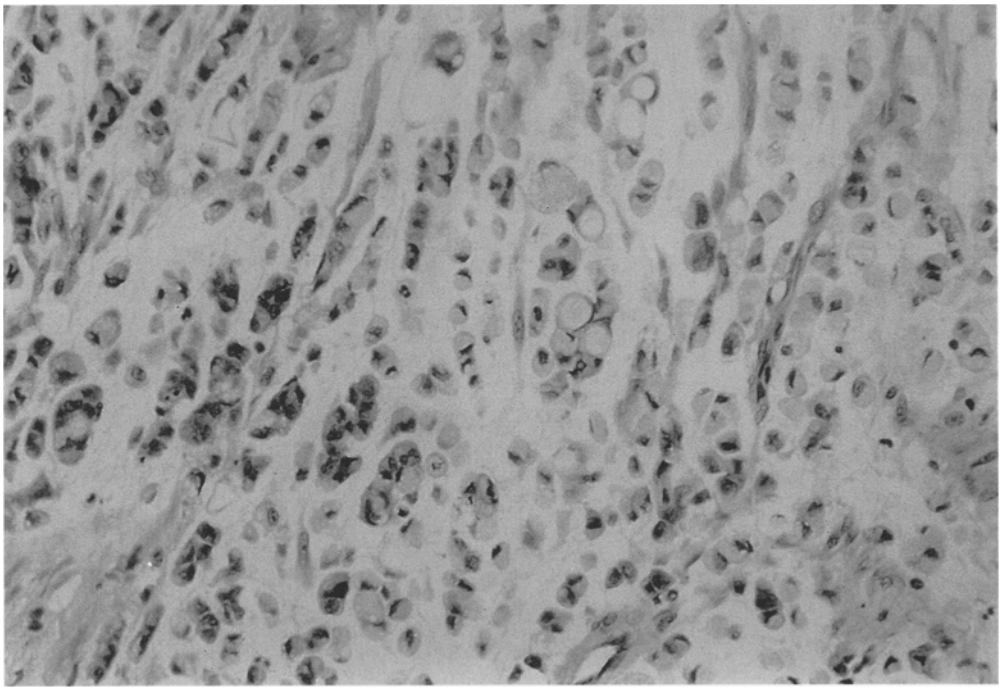


Fig. 1 Cystoplasty adenocarcinoma with prominent signet ring pattern. H&E, ×400

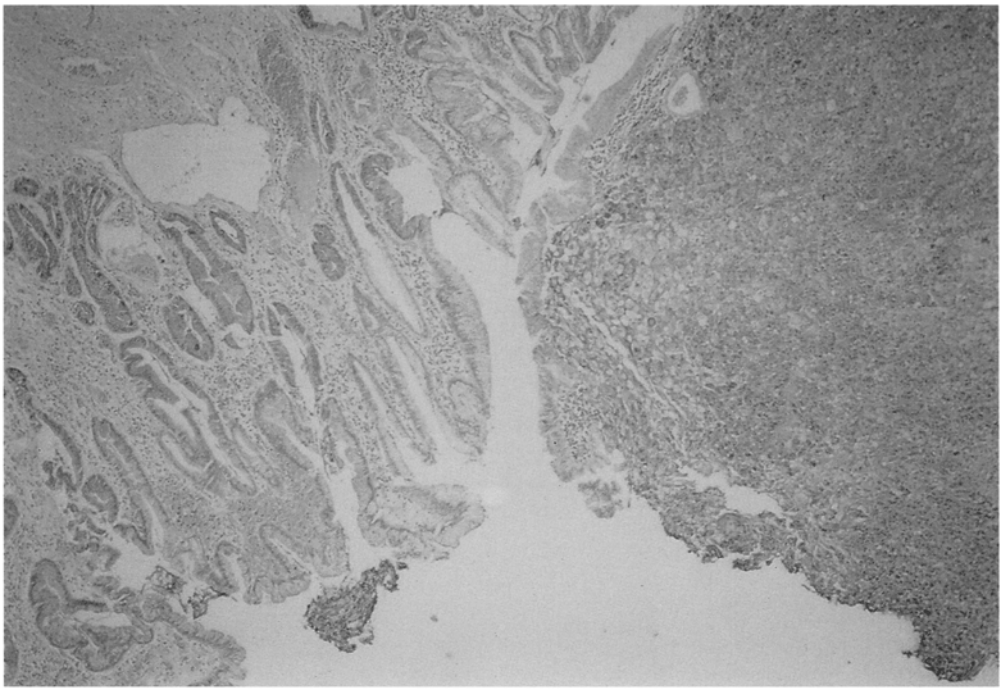


Fig. 2 Gradation of abnormal mucin staining from normal gut (*left*) to adenocarcinoma (*right*). PNA-HRP/neuraminidase, ×100

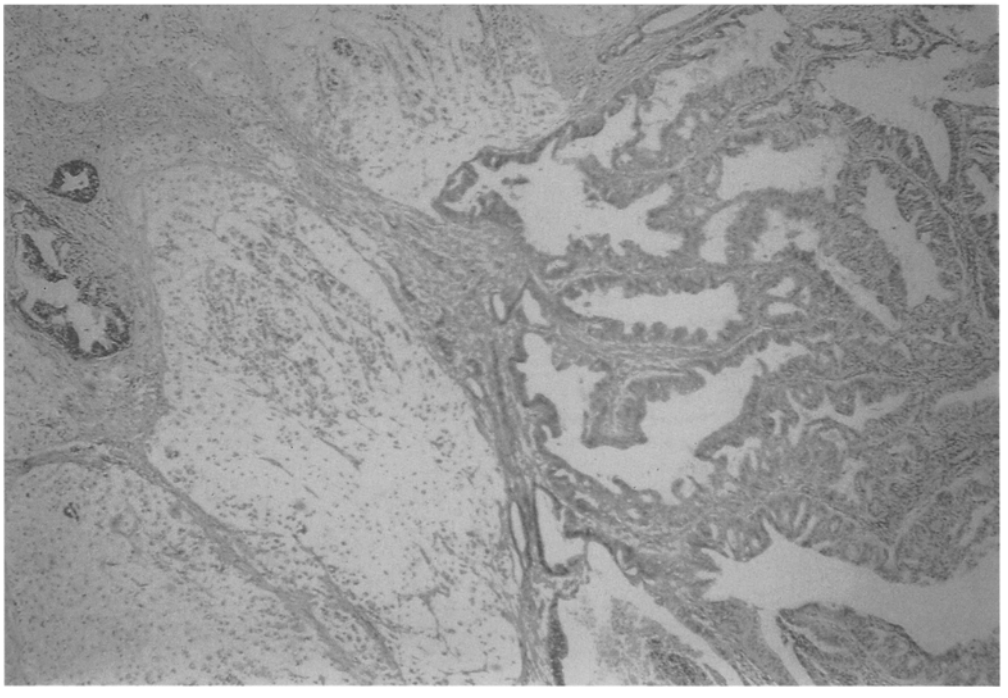


Fig. 3 Papillary transitional cell carcinoma overlying sheets of palely staining, infiltrating adenocarcinoma. H&E, ×100

Four of the five cases studied were confirmed to be high-grade adenocarcinomata and a number of factors suggest that these malignant tumours may be of gut origin. Two of the tumours showed a prominent signet-ring architecture (Fig. 1). Whilst this type of adenocarcinoma is relatively common in gastrointestinal malignancy, it is extremely rare as a primary bladder neoplasm [10]. The patient with a caecocystoplasty showed the graduated increase in sialomucin production from normal colonic to malignant mucosa typical of a right-sided colonic carcinoma. The pattern in the ileocystoplasties was of a gross increase in the staining for sulphomucin. There was no significant mucus staining in any of the bladder remnant biopsies. Abnormal carbohydrate lectin staining was seen in all the carcinomas with particularly heavy staining with PNA-HRP. This staining also showed gradation from normal to abnormal

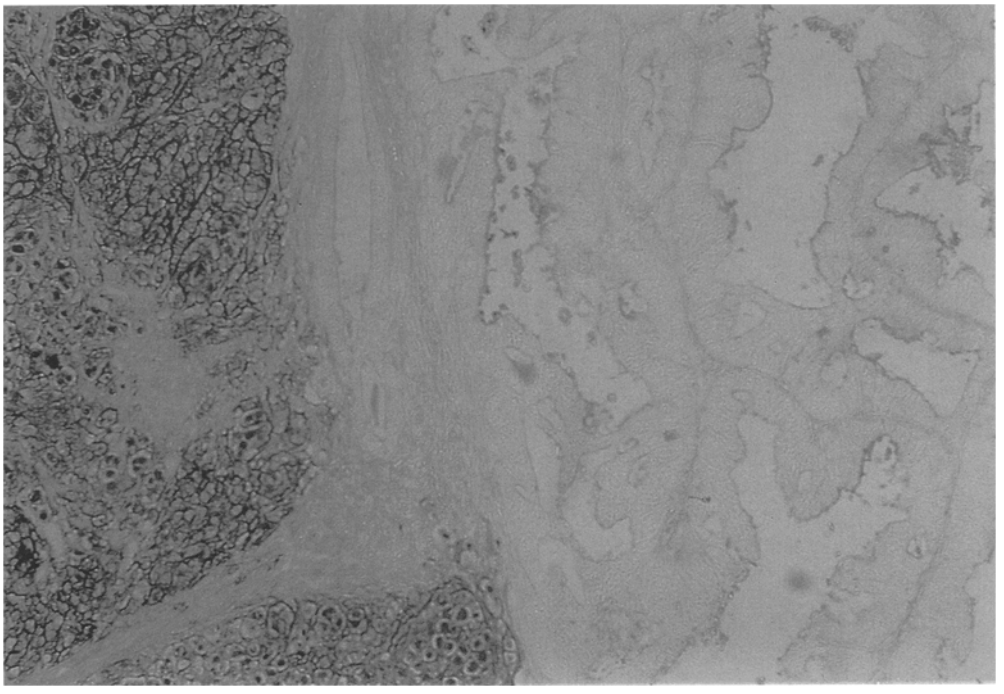
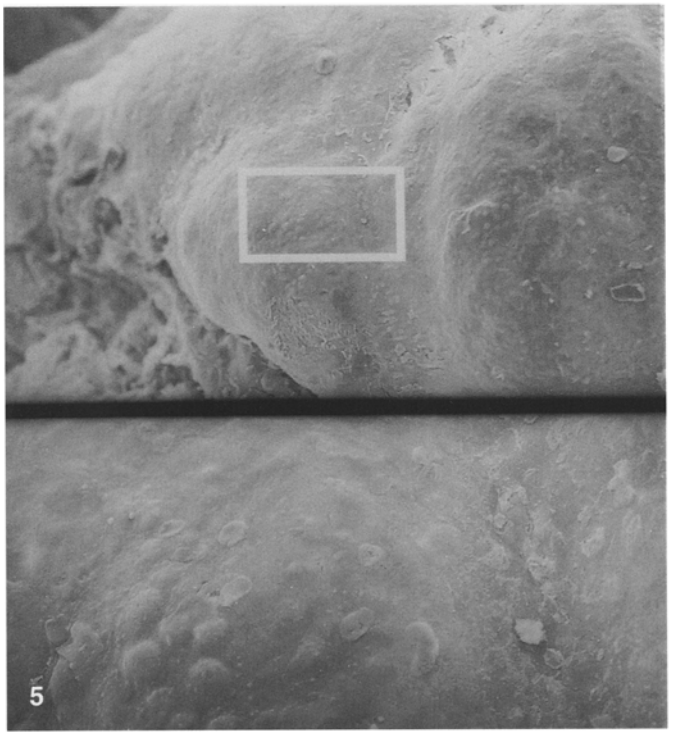


Fig. 4 Intense mucin staining of adenocarcinomatous cells infiltrating beneath unstained papillary TCC. ABPAS, ×100



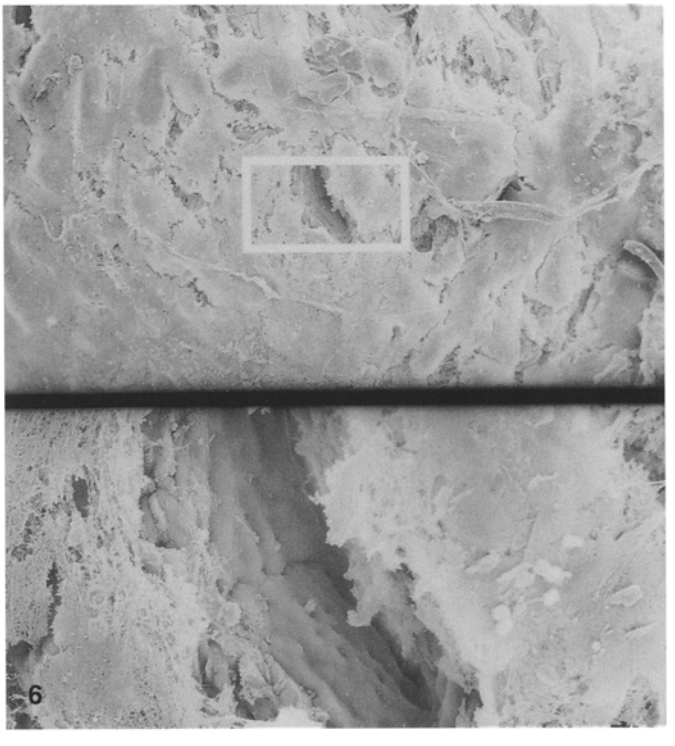


Fig. 5 Intact mucus coating on normal colonic mucosa (laparotomy specimen. SEM ×100 and 400

Fig. 6 Fragmented mucus coat exposing mucosa in biopsy from patient 56 months after caecocystoplasty. SEM, ×100 and 400

intestinal mucosa (Fig. 2) and was enhanced by pre-treatment with neuraminidase to remove sialic acid. One case contained a previously unreported papillary transitional cell carcinoma adjacent to the adenocarcinoma (Fig. 3). There was no significant labelling of the transitional cell tumour for mucin despite heavy staining of the underlying adenocarcinoma (Fig. 4).

These histochemical staining patterns suggest that the adenocarcinomata in these patients are arising from the intestinal element of the enterocystoplasty. However, this interpretation must be tempered with a degree of caution. Newbould and McWilliam [8] examined a series of primary vesical transitional and adenocarcinomata using the same mucin staining techniques as in this study in addition to benign conditions such as cystitis cystica. In their specimens, sialo- and sulphomucins were present in both intestinal metaplasia and cases of cystitis cystica with intracellular mucin production. A proportion of transitional cell tumours also demonstrated sialomucin secretion. Six of their nine cases of primary vesical carcinoma showed a colonic type profile of mucin staining. Barresi and Marafioti [1] have also reported a sialomucin-positive TCC arising in continuity with intestinal metaplasia of the bladder. The development of adenocarcinoma, at or adjacent to the anastomosis in ureterosigmoidostomy, is well recognised but has previously been thought to be due to the admixture of urine and faeces. Urine alone, however, can promote malignant change at colovesical anastomoses in an animal model [16]. In that study the development of tumour was preceded by a fourfold increase in crypt cell production rate. A similar increase in the number of crypt cells is also seen in biopsies from patients who have undergone caecocystoplasty (K Murray, personal unpublished data). Under normal circumstances intestinal mucosa is protected by a continuous layer of secreted mucus. Breakdown of this mucus coat has been observed adjacent to and over the surface of orthotopic colonic tumours [17]. A similar change from a complete mucus coating (Fig. 5) to a fenestrated appearance with exposure of the underlying mucosa (Fig. 6) has been observed, using scanning electron microscopy (SEM), by the authors in patients who have previously undergone caecocystoplasty. If this exposure of the intestinal mucosa is then combined with the high levels of urinary *N*-nitrosamines found in cystoplasty patients [9], an aetiological pathway can be proposed for the occurrence of enterovesical anastomotic tumours similar to those seen after ureterosigmoidostomy [13]. It is interesting that the lag time for tumour development is similar in the two groups of patients [14].

In conclusion it appears that endoscopic follow-up of patients undergoing enterocystoplasty should include anastomotic biopsy and, if available, histochemical assessment of both bladder and bowel mucosa for evidence of premalignant change.

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