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Histological Changes in the Urinary Bladder Secondary to Urethral Catheterisation

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Summary-The macroscopic and microscopic features of the urothelial response of the human urinary bladder to urethral catheterisation are described. The catheter reaction is characterised by a predominantly eosinophilic inflammatory response producing, macroscopically, a papillary mucosal appearance termed polypoid cystitis. The severity of the epithelial inflammatory response correlates significantly with the duration of catheterisation. Urotheliaf dysplasia confined to the catheter reaction site was noted in 6% of cases. The possible implications of these findings are discussed.

The cytoscopic appearances of the urothelial re· sponse to the irritative effects of an indwelling urethral catheter are well recognised by urologists. Indeed, it is perhaps because of this familiarity that there have been relatively few histopathological descriptions of the catheter reaction in the literature (Ekelund *el a/.*, 1983). The macroscopic differentiation of a catheter reaction from a papillary transitional cell carcinoma can be extremely diffi· cult, if it were not for the preceding history of catheterisation. This difficulty was remarked on by Friedman and Ash (1959), who first described polypoid cystitis, a term subsequently used by Ekehmd and Johannson (1979) to describe the histopathological changes of the catheter reaction. Recent concern over the toxicity of catheter eluates {Talja *et al.*, 1985) and the carcinogenic potential of the irritative effect of urethral catheters (Murphy *eta!.*, !986) prompted this investigation. A prospective study of 30 consecutive catheterised patients undergoing transurethral prostatectomy was con· ducted. A possible role for catheter-induced urothelial hyperplasia in urothelial carcinogenesis is discussed.

Patients and Methods

AU 30 patients entered into the study had beer. catheterised for acute retention of urine secondary to benign prostatic hypertrophy. Their mean age was 73 years (range 58-84). They had been catheterised for between 2 days and 3 years, often with a variety of Silastic and latex rubber catheters. The catheters were removed on the morning of surgery and a catheter specimen of urine sent for bacteriological examination.

Cystoscopic evaluation of the catheter reaction was performed prior to transurethral prostatectomy. The severity of the reaction was graded as mild, moderate or severe. The site of the catheter reaction was recorded. Biopsies were then taken using cold-cup biopsy forceps (Storz) from the site of maximal reaction and from bladder mucosa elsewhere which, macroscopically, was most nor mal in appearance. Samples were randomly labelled A and B and the aHocation recorded in the operation notes.

Paraffin-embedded 5!1 sections of the biopsies were stained with haematoxyHn and eosin and Perls' stains. Histological examination of the samples was performed without the observer knowing details of site, cystoscopic findings or the duration of preceding catheterisation. The severity of the mucosal inflammatory reaction was graded using u semiquantitative scale where 0= none, 1 = focal lymphocytic infiltration, 2=diftuse predominantly lymphocytic infiltration, 3=diffuse predominantly eosinophil polymorphonuclear infiltmtion and 4=grade 3 changes in combination with intra-epithelial eosinophilic micro-abscesses. The histo-

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pathological grades were correlated with the duration of catheterisation (days) using the Wilcoxon rank sum test and with the presence or absence of associated bacterial infection using Student's *t* test.

Results

The cystoscopic appearances were graded as severe in 11 cases (37%), consisting of a raised, oedematons, haemorrhagic papiJlary mucosal abnormality most prominent on the posterior bladder wall and often involving adjacent surfaces of the collapsed bladder. The reaction was mild or absent in 3 patients (10%) and moderate in 16 (53%).

Histological differences between the two biopsies (A and B) were noted in 26 patients(86%);"normal" mucosa was abnormal in 8 patients (26%) with the appearances of acute on chronic cystitis. Low power microscopy of the severe catheter reactions revealed broad-based, oedematous mucosal papillae conforming to the classical description of polypoid cystitis (Fig. 1). The catheter reaction consisted of a mucosal inflammatory response rich in eosinophil granulocytes in 26 patients (86%) with intra-epithelial micro-abscesses in 9 patients (30}'J (Fig. 2}. Urothelial hyperplasia was present in 11 patients (36%). Moderate urothelial dysplasia, confined to the biopsy taken from the area of maximal reaction, was present in 2 patients (6%), both of whom had been catheterised for >4 months (122 and 146 days) (Fig. 3). Acute inflammatory changes were absent in 3 patients(lO%); iron-laden macrophages in the lamina propria, indicating previous haemorrhage, were found in 2 patients (6 .,). Neither urothelial necrosis nor squamous metaplasia was identified in any of the biopsies.

There was a statistically significant correlation between the grade of mucosal inflammatory re·

Fig. I Polypoid cystitis. (H and E x 33).

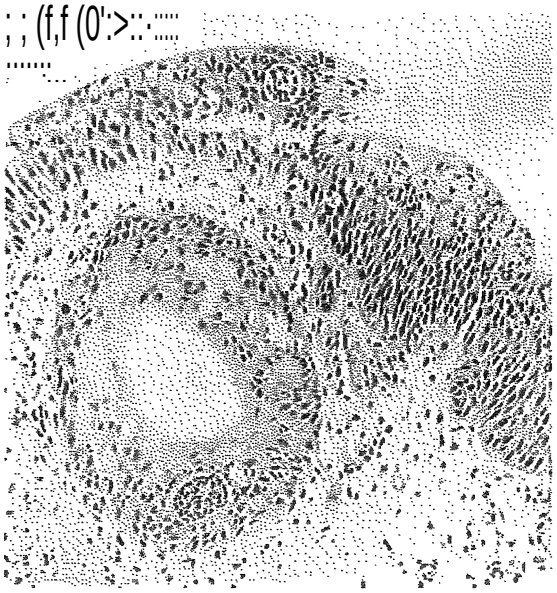
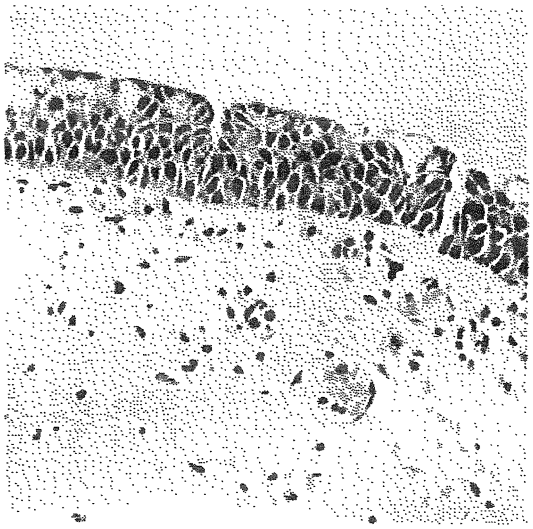


Fig. 1 Bladder urothelium showing epithelial hyperplasia. cystitiscystica and intra-epithelial eosinophilic micro-abscesses. (Hand E x 360).



FJg. 3 Urothelium showing moderately severe urothelial dysplasia. (H and E x 250).

sponse (>grade 2 *vs* <grade 3) and the duration of catheterisation (P<O.OS). No patient who had been catheterised for less than l month showed evidence of intra epitheliai micro abscesses (grade 4). There was no correlation between the severity of the mucosal inflammatory response and the presence or absence of associated bacterial infection. There was a good correlation between the cystoscopic appearances and the histological findings; of the 11 patients with a severe reaction on cystoscopic assessment, 9 had grade 4 and 2 had grade 3 urothelial inflammatory changes.

Discussion

The catheter-associated urothelial histological changes described in this series were very similar to those described as polypoid cystitis by Ekeh.md and Johannson (1979). However, they did not comment on the presence of eosinophils in the inflammatory response, which was described as consisting of neutrophils, lymphocytes and inflammatory cells. Indeed, the abundance of eosinophils in the urothelial inflammatory response, secondary to the stimulus of catheter irritation, has previously been reported only in animal experiments. Talja *et al.*(1985) noted an inflammatory infiltrate, consisting of 80% eosinophil polymorphs, around strips of catheter material implanted into the dorsal muscle of rabbits for 4 days. The marked eosinophilia of the catheter reaction in humans is almost certainly due to the presence of mast cells in the lamina propria of the urinary bladder mucosa. Following surface lgE-mediated antigenic stimulation, mast cells degranulate and release acidic tetrapeptides which attract and immobilise eosinophils (Holgate, !983). Furthermore, in our study, the severity of the epithelial response correlated with the duration of catheterisation. In effect, therefore, the predominantly eosinophilic infiltration occurs after an initial lymphocytic response, reaching a peak approximately 4 weeks after catheterisation.

This feature is similar to the intestinal mucosa! response to parasitic infection (Roitt *et al.*, 1985) in which there is an initial. sensitising period of 2 to 3 weeks following exposure of the non-toxic parasitic antigens. These antigens stimulate T ceUs and macrophages to interact with B cells producing IgE-spedfic antibody. Both IgE and mast cell precursors then accumulate in local lymph nodes. The mast cells then acquire parasite antigen·specifi.c IgE on their surface and return to the mucosa, where they degranulate on contact with the antigen, releasing the eosinophil chemotactic factors. In the case of the urothelial response the analogous antigen may well be the catheter substance. Furthermore, there was no correlation between the presence or absence of associated bacterial infection and the severity of the urotheHal inflammatory response. This confirms the findings of Ekelund and Johannson (1979), who noted that the severity of the polypoid cystitis was not influenced by bacterial urinary tract infection. C.atheter*associated polypoid cystitis, therefore, appears to be a direct response of the mucosa to the catheter *per se*, probably following a period in which an immunological response is mounted against catheter-derived antigens.

The chronic irritativeeffectofindwelHng urethral catheters in rats has been shown to be a strong stimulus for the induction of urothelial neoplasia (Murphy *et al.*, 1986).The constant irritative action on the urothelium may have a promotor-like effect of inducing urothelial hyperplasia, identified in 36% of cases in our study. Persistent hyperplasia would allow neoplastic growth of latent urothelial tumour cells, previously transformed by sub-threshold doses of urinary carcinogens. Just as epithelial hyperplasia in the eal'ly experimental stages of skin carcinogenesis was reversible (Hicks, 1980}, so was the urothelial hyperplasia of the catheter reaction found to be reversible (Ekelund *et al.*,1983). Indeed, Murphy *et al.* (1986) suggested a two-stage process of irritative urothelial carcinogenesis, with papillary hyperplasia being the first, potentially reversi·bJe, stage. The development of squamous cell carcinoma of the urinary bladder, arising in matapiastic squamous bladder mucosa, in association with long-term catheterisation is well recognised (Kaufman *et al.*, 1917; Locke *et al.*, 1985), with an incidence of 8 to 10% following catheterisation for at least 10 years. In the development of these tumours, however, the latent period before the hyperplasia becomes irreversible and the relationship of this change to the occurrence squamous metaplasia have yet to be elucidated. The finding of dysplasia in association with the catheter reaction has not previously been reported and although the association is possibly coincidental, it is obviously of considerable importance in this context.

In conclusion, the acute catheter reaction is typically a localised polypoid cystitis characterised by an eosinophilic infiltrate secondary to what is presumed to be the toxic, irritative effects of urethral catheters. This reaction may also be partly mediated by an immunological sensitisation to the catheter substance. Catheter-associated urothelial

hyperplasia and dysplasia are probably relevant to the development of bladder tumours in patients with tong-term indwelling catheters.

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