Comparative pathology of dome and trigone of urinary bladder mucosa in paraplegics and tetraplegics

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Paraplegic/tetraplegic individuals are prone to develop chronic urinary tract infection, urinary calculi and bladder outlet obstruction, and have a 16 to 28 times higher risk for squamous cell bladder cancer. The preferable method of monitoring those patients who are at high risk of developing vesical neoplasia has been an annual check-up inclusive of cystoscopy and cold cup bladder biopsy of all suspicious areas as well as predetermined random sites. It may be desirable to take a biopsy from one site (when there is no suspicious lesion) with a flexible cystoscope while the patient is sitting in the wheelchair itself in the outpatient clinic instead of multiple biopsies from the dome, trigone and both lateral walls of the urinary bladder taken in the operation theatre set-up using a rigid cystoscope with the patient positioned in lithotomy. Before adopting such a cost-saving and more convenient procedure routinely, we evaluated whether any significant additional histopathological findings are obtained by taking bladder biopsies from the dome and the trigone of the urinary bladder instead of just one, be it dome or trigone in the absence of any visible urothelial lesion in the bladder. In forty consecutive tetraplegic/paraplegic patients who did not have any cystoscopically distinguishable urothelial neoplastic lesion such as papilloma, cold cup biopsies of the dome and the trigone were taken randomly before carrying out any diagnostic or therapeutic procedure, eg electrohydraulic lithotripsy of vesical calculi. All the biopsy specimens were evaluated by a pathologist who was unaware of the clinical details and not involved with the primary diagnosis. In 15 cases, significant additional histopathological finding(s) were recorded in the trigone biopsy which were not seen in the dome biopsy (follicular cystitis: $n = 4$; squamous metaplasia: $n = 4$; extensive squamous metaplasia with focal atypia: $n = 1$; limited focal atypia: $n = 1$; extensive glandular metaplasia: $n = 1$; intestinal metaplasia and possibly follicular cystitis: $n = 1$; and follicular cystitis and intestinal metaplasia: $n = 1$; mild atypia: $n = 1$; extensive calcification of epithelial denudation: $n = 1$). Histopathology of dome biopsies revealed significant additional histopathological finding(s) in nine cases (follicular cystitis: $n = 2$; squamous metaplasia: $n = 2$; intestinal metaplasia: $n = 1$; squamous metaplasia and adenomatoid metaplasia and mild atypia: $n = 1$; features of interstitial cystitis: $n = 1$; mild dysplasia: $n = 1$; mild crypt hyperplasia of urothelium with mild atypia: $n = 1$). Thus in twenty cases (50%), significant additional findings were obtained by taking cold cup random biopsy of the dome as well as the trigone in the absence of any visible morphological changes. Although single site biopsy may be less traumatic, more convenient to the patient as well as to the staff, and cost-saving, in the spinal cord injury patients with neuropathic bladder, it may not be diagnostically adequate even in those patients who do not have any cystoscopically distinguishable lesion in the urinary bladder.

Keywords: spinal cord injury; neuropathic bladder; bladder biopsy; paraplegia; tetraplegia

Introduction

Paraplegic individuals are prone to develop chronic urinary tract infection, urinary calculi, vesical outlet obstruction and have been shown to have a 16 to 28 times higher risk for squamous cell bladder cancer.¹ The malignant potentiality of the urothelium in neuro-

pathic bladder following spinal cord injury is well recognised. Its incidence in the spinal cord injury population has been reported to be 2.3%.² These tumours are 460 times more common than bladder tumours in the general population.² The increased occurrence of bladder tumours correlates with the duration of urothelial inflammation, chronic urinary tract infection, vesical stone, and indwelling catheter drainage of the urinary bladder. It may be desirable to

monitor those patients who are at high risk for developing bladder tumours by annual check-ups inclusive of cystoscopy with cold-cup biopsies of all suspicious areas as well as predetermined random sites. With the availability of flexible cystoscope, urothelial biopsies of the lower urinary tract can be obtained using a 16 Fr actively deflectable, flexible cystoscope and the 5.4 Fr Thermo Jaw Hot Urologic Forceps (Microvasive Corp., Watertown, MA, USA). This biopsy forceps allows simultaneous tissue sampling and electrocoagulation of the biopsy site.³ We have been performing flexible cystoscopy in the spinal cord injury patients as they are sitting on the wheelchair in the outpatient clinic. Previously, when cystoscopy was performed with a rigid cystoscope, the patient had to be undressed, transferred on to a trolley with the help of a hoist, taken to the operation theatre, and positioned in lithotomy taking suitable precautions to avoid pressure markings; some will require ROHO cushion on the trolley also while being transferred to the operation theatre as well as on the operation table as their skin may be very vulnerable to developing pressure marks; all patients will require adequate padding of the leg while being positioned in lithotomy. After cystoscopy, these steps are again performed in reverse order which takes considerable time, and requires significant nursing in-pat. In contrast, the technique of flexible cystoscopy has proved to be more convenient to the patient, his/her carers and the hospital staff. If single biopsy is taken from the bladder say, from the trigone or from the dome, the morbidity of the procedure in terms of bleeding, perforation, etc is minimised. The cost of operation theatre use, tissue processing and interpretation are reduced as well. The procedure may then be carried out as an outpatient without requiring hospital admission. Thus the cost of this annual check-up can be reduced. In patients in whom no suspicious areas are seen during cystoscopy, single biopsy with a flexible cystoscope may be a cost-saving proposition. However, we preferred to investigate whether biopsy from a single site in the absence of any morphologically visible abnormality during cystoscopy would prove to be a representative sample providing adequate information from a diagnostic view point. We therefore investigated prospectively whether taking biopsies from the dome as well as trigone in the spinal cord injury persons who did not have any cystoscopically visible neoplastic lesion in the neuropathic urinary bladder provided any additional significant histopathological information in comparison to a biopsy taken from the dome alone or from the trigone alone.

Patients and methods

Forty consecutive adult spinal cord injury patients who were otherwise scheduled for a cystoscopy prior to treatment of bladder stone(s) ($n = 20$), urethral diverticulum ($n = 2$), urethral calculus ($n = 1$), urethral stricture ($n = 1$) and prostatic urethral calculus ($n = 1$), division of external urethral sphincter and transurethral resection of bladder neck ($n = 3$), inser-

tion of JJ ureteral stent (as the initial step before shock wave lithotripsy of renal calculus) ($n = 3$); or for evaluation of haematuria ($n = 8$); or prior to performing ascending ureterophyelography in a case of pelvi-ureteric junction obstruction were the subjects of this study. The nature of the investigation was explained to the patient and to his/her carer(s) and written informed consent was obtained. Cystoscopy was performed with a Storz 22 Fr rigid cystoscope in the lithotomy position. Cold-cup biopsy was taken randomly under vision from the dome and from the trigone of the urinary bladder. Any bleeding point was then fulgurated with diathermy electrode.

Tissue processing, histology

Bladder biopsies were fixed by immediate immersion in 0.1 M, phosphate buffered, 4% formaldehyde, pH 7.4 for a minimum of 6 and a maximum of 12 h. After dehydration, specimens were routinely processed to paraplast using vacuum processing and a maximum temperature of 53 °C. Five micron sections were cut and mounted routinely for haematoxylin and eosin staining. All the biopsy specimens were evaluated together by a pathologist who was unaware of the site of biopsy and of relevant clinical details. The histopathological findings of the dome and trigone biopsy were then compared to find out whether any significant additional information is obtained by taking biopsy specimens from two sites instead of just one, be it from the dome or from the trigone in the absence of any cystoscopically visible lesion in the urinary bladder.

Pathological classification

For the purpose of this study, the architectural changes of epithelium were defined as follows.

Dysplasia Urothelium, with or without hyperplastic or hypoplastic features, showing disruption of the normal pattern of decreasing nuclear size with migration through the layers upward.

Metaplasia Change of urothelium into either epithelium resembling intestinal lining or squamous epithelium of the non-keratinizing type.

Atypia Loss of normal architectural aspect of 'maturation', ie (abnormally) large and hyperchromatic nuclei in superficial position, abnormal mitotic figures in superficial position, etc.

Follicular cystitis The presence in the submucosa, but directly in apposition to the urothelium, (considerable numbers) of lymphoid follicles with active follicle centre reaction and well developed mantle zone.

Interstitial cystitis The presence of inflammatory infiltrate, inclusive of a significant component of eosinophilic polymorphonuclear cells, not only superficially but also within the deeper layers of smooth muscle.

There is a significant increase of mast cells within the stroma.

Results

The performance of a bladder biopsy did not impose any additional morbidity in any of the 40 patients. None of these 40 patients had any cystoscopically visible urothelial neoplastic lesion in the urinary bladder such as papilloma. Those patients who were on indwelling urethral catheter drainage had mildly inflamed mucosa. Patient 1 (dob: 10-04-1944) who was on indwelling catheter drainage had an ulcerated lesion in the trigone and biopsy taken from that site showed non-keratinizing squamous epithelium of 'vaginal' type; the appearances were consistent with vaginal metaplasia of the bladder trigone. In sixteen patients, varying degrees of inflammatory changes were observed in the biopsy specimens from the dome as well as from the trigone without any other well-defined histopathological abnormality, eg squamous metaplasia or follicular cystitis. In four patients, similar histopathological finding was observed in biopsies of dome as well as of the trigone (follicular cystitis in two cases; denuding cystitis in one case; and squamous metaplasia in one). In twenty patients (50%), significant additional histopathological finding was obtained by taking biopsies both from the dome and from the trigone (Table 1). The clinical details of these 20 patients are given in Table 2.

By comparing the histopathological findings of the biopsy from the trigone with that of the dome, in 15 cases, significant additional histopathological findings were recorded in the trigone biopsy which were not seen in the dome biopsy (follicular cystitis in four cases; squamous metaplasia in four cases; virtually complete, extensive squamous metaplasia with focal atypia in one case; limited focal atypia in one case (this patient had extensive crypt metaplasia in the trigone biopsy and intestinal metaplasia in the dome biopsy); glandular metaplasia in one case; intestinal metaplasia and possibly follicular cystitis in one case; follicular cystitis and intestinal metaplasia in one case; mild atypia in one case; extensive calcification of epithelial denudation in one case).

By comparing the histopathological findings of the biopsy from the dome with that obtained from the trigone, significant additional histopathological finding(s) were recorded in nine cases (follicular cystitis in two cases; squamous metaplasia in two cases; intestinal metaplasia in one case; squamous metaplasia and adenomatoid metaplasia and mild atypia in one case; features of interstitial cystitis in one case; mild dysplasia in one case; and mild crypt hyperplasia of urothelium with mild atypia in one case which was seen in the dome biopsy only whereas features of follicular cystitis were observed in dome as well as trigone biopsies). Four representative cases are illustrated in Figures 1 to 4 in whom significant additional histopathological finding(s) was obtained by taking biopsies from the dome as well as from the trigone. Thus in 20 out of 40

cases (50%), significant additional findings were obtained by taking cold cup random biopsy of the dome as well as the trigone in the absence of any visible morphological changes in the urinary bladder.

Discussion

Spinal cord injury patients with indwelling urethral catheters or those with a suprapubic cystostomy are prone to have an increased incidence of complications in comparison to patients who are managed without an indwelling catheter. Apart from the well recognised and frequently encountered complications such as chronic and acute cystitis, pyelonephritis, renal calculi, vesical calculi, urethritis, periurethral abscess, epididymitis, and orchitis, bladder cancer, especially squamous cell carcinoma, occurs with a greater incidence in those spinal cord injury patients managed with an indwelling catheter drainage for a long period of time. Kaufman *et al*¹ studied 25 spinal cord injury patients with permanent bladder catheters for more than 10 years. Vesical malignancy was observed in five cases (20%). Locke *et al*⁴ assessed prospectively by bladder biopsy 25 consecutive spinal cord injury patients catheterised for a minimum of 10 years. Two cases of squamous cell carcinoma of the bladder were identified. Yalla's⁵ experience with 15 cases of squamous cancer in spinal cord injury patients is more pessimistic, since three of these patients had negative cytology results. Of the 15 patients with squamous cell carcinoma, 13 patients were found to have invasive tumours at diagnosis. To make matters worse, one of these 15 patients with negative cytology and biopsies at the annual evaluation had large exophytic squamous cancer with liver metastases before the subsequent examination. This unpredictable lethal behaviour of these cancers suggests the need to diagnose and treat the predisposing factors in these cases. Apart from indwelling urinary catheters, chronic urinary tract infection, bladder stones, and urinary stasis associated with a neuropathic bladder are recognised predisposing factors for the development of bladder cancer. Urine cytology and ultrasonography may be unreliable to detect vesical malignancy in the presence of urinary infection, cystitis, and inflammatory bladder wall thickening. A thorough urological evaluation must include cystoscopy and bladder biopsy.⁶ Cystoscopy and biopsy should be performed at the very least on a yearly to every-two-year basis. This recommendation is supported by the number of cases of carcinoma diagnosed on routine biopsy where no suspicious lesion existed cystoscopically.⁷

In a spinal injury centre managing say 4000 cases of spinal cord injury, a protocol of annual cystoscopy and bladder biopsy with hospitalisation of 2 days imposes additional financial burden on the already depleted resources. The vast majority of these patients may not have any cystoscopically visible urothelial lesion. It is therefore, tempting to do the minimum without compromising the quality of patient care. In this context, we evaluated whether a single random biopsy from the urinary bladder when no suspicious areas are identified

Table 1 Histopathology of the urinary bladder biopsies from the dome and from the trigone of paraplegic/tetraplegic patients in whom significant additional findings were seen either in the dome or in the trigone biopsy

<i>Patients</i>	<i>Present method of urinary bladder drainage</i>	<i>Histopathology of urinary bladder dome biopsy</i>	<i>Histopathology of urinary bladder trigone biopsy</i>
1	Indwelling urethral catheter drainage for 5 years; no catheter for 3 months	Follicular cystitis	Complete squamous metaplasia
2	Penile condom drainage Bladder stone	Moderately dense inflammatory infiltrate with tendency to follicular aggregation without active follicle centre reaction	Extensive early intestinal metaplasia Follicular cystitis
3	Penile condom drainage Renal calculus	Early stages of squamous metaplasia	Limited oedema and small vessel proliferation with completely absent inflammatory infiltrate
4	Intermittent self-catheterisation. Bladder stones	Follicular cystitis	Squamous metaplasia. Moderately active follicular cystitis
5	Indwelling urethral catheter drainage since November 1994	Extensive crypt metaplasia with early squamous metaplasia changes	Early signs of intestinal metaplasia. Occasionally lymphoid aggregates develop the aspect of follicles with occasionally recognisable lymphoid follicle centre. Possibly follicular cystitis
6	Penile condom drainage	Follicular cystitis	Limited glandular metaplasia
7	Indwelling urethral catheter drainage since November 1993	Early squamous metaplasia with mild atypia. Focal adenomatoid metaplastic changes	There is inflammatory infiltrate of polymorphonuclear cells and lymphocytes within the urothelium
8	Penile condom drainage Prostatic urethral calculi	The submucosal stroma shows superficial inflammatory infiltrate with lymphocytes and mature plasma cells and occasional polymorphonuclear cells that invade the superficial lining epithelium	Follicular cystitis
9	Penile condom drainage Vesical calculus and bulbar urethral stricture	Bladder mucosal biopsy with openings into deep crypt glands in which almost intestinal type omphocytic metaplastic changes are seen	There is dense submucosal inflammatory infiltrate in which lymphocytes, plasma cells and considerable numbers of polymorphonuclear cells are seen
10	Indwelling urethral catheter drainage since September 1983. Vesical calculi	Signs of interstitial cystitis and/or allergic component	Virtually complete, extensive squamous metaplastic change with extensive koilocytotic abnormalities of the cytoplasm. Focal atypia
11	Indwelling urethral catheter drainage since 1985. Vesical calculi	The lining epithelium is flattened and the submucosal connective tissue shows dense inflammatory infiltrate consisting mainly of lymphocytes and mature plasma cells	Extensive squamous metaplastic change of the lining epithelium
12	Intermittent self-catheterisation. Vesical calculus	Limited inflammatory infiltrate with perivascular distribution consisting mainly of lymphocytes	Follicular cystitis
13	Intermittent self-catheterisation. Bladder stone	There is considerable degree of oedema with inflammatory infiltrate in which in addition to lymphocytes, many polymorphonuclear cells are seen	Follicular cystitis
14	Indwelling urethral catheter drainage since July 1993 Bladder stone	Basement membrane shows diffuse inflammatory infiltrate mainly of lymphocytes and plasma cells	Follicular cystitis

Table 1 (Cont)

<i>Patients</i>	<i>Present method of urinary bladder drainage</i>	<i>Histopathology of urinary bladder dome biopsy</i>	<i>Histopathology of urinary bladder trigone biopsy</i>
15	Indwelling urethral catheter drainage. Multiple bladder stones	Superficial inflammatory infiltrate of mixed nature containing, amongst others, considerable numbers of polymorph	Bladder mucosal biopsy shows intense encrustation of necrotic debris and denuded surface with fibrin deposition. Extensive calcification of epithelial denudation
16	Penile condom drainage	Mild dysplasia	Slight follicular perivascular aggregates of lymphocytes and other inflammatory cells
17	Indwelling urethral catheter drainage since September 1992. Urethral diverticulum	There is a diffuse inflammatory infiltrate consisting of many lymphocytes and plasma cells with a considerable increase in the number of mast cells. Elsewhere there is almost haemangiomatic proliferation of granulation tissue with many small capillaries and iron laden macrophages	Urinary bladder biopsy with nested proliferation and in between nests three or four cell layers are left. Intact umbrella cells are seen. In the nested cells there is a considerable degree of dyskeratosis with uneven cells with irregular nuclear shapes and sizes distributed throughout the epithelium with some loss of organisation and maturation. Mitotic figures are not seen higher in the epithelium and occasional polymorphonuclear cells are seen to invade. Mild atypia
18	Intermittent catheterisation Bladder calculus	There is perivascular inflammatory infiltrate of mixed cellular nature and within the connective tissue stroma occasional areas of haemorrhage. A number of sections show abnormally thick walled blood vessels. Denuding cystitis	Early squamous metaplasia. There is a profuse proliferation of small blood vessels giving almost the impression of oedematous granulation tissue with occasional perivascular aggregates of lymphocytes and occasional polymorphonuclear cells
19	Indwelling urethral catheter drainage for 9 years. At present practising intermittent catheterisation	Intestinal metaplasia	Limited focal atypia. Extensive crypt metaplasia
20	Indwelling urethral catheter drainage since January 1994	Follicular cystitis. Mild crypt hyperplasia of urothelium with mild atypia	Active follicular cystitis

cystoscopically would be diagnostically adequate as it would obviously mean less morbidity to the patient who is otherwise asymptomatic. But we found that although single site biopsy may be less traumatic, more convenient to the patient as well as to the staff, and cost saving, in the spinal cord injury patients with neuropathic bladder, it may not be diagnostically adequate even in those patients who do not have any cystoscopically distinguishable lesion in the urinary bladder.

Atypia was noted in five patients on indwelling urethral catheter drainage; in three of them atypia was observed only in the biopsy taken from the trigone whereas it was observed in the biopsy taken from the dome only in two cases. Dysplasia was observed in the biopsy taken from the dome only in another patient who was on penile condom drainage. Thus differences in urothelial proliferation and differentiation were observed between the trigone and dome areas of the neuropathic bladder in the same individual. Van Velzen *et al*,⁸ while studying the proliferation status of urothelium in spinal cord injury persons in order to

find out the peculiarities of the neuropathic bladder which make it vulnerable to recurrent cystitis, observed significant differences in urothelial proliferation between the trigone and the dome region when the bladder biopsy specimens were studied by immunohistochemical methods (by labelling for proliferating cell nuclear antigen (PCNA-10) and Ki 67 antigen (using the monoclonal antibodies suitable for detection of the recombinant DNA based MIB-1 fragment of the Ki 67 antigen). For example, in the case of patient 1 an incomplete tetraplegic, virtually complete PCNA/MIB-1 dissociation with proliferative arrest was observed in the biopsy specimen taken from the dome whereas in the biopsy specimen taken from the trigone of the same patient, no signs of PCNA/MIB-1 dissociation or proliferation arrest were observed. Similarly, while studying epidermal growth factor receptor (EGF-R) expression in the vesical urothelium of spinal cord injury patients, Parsons *et al*⁹ noted discrepancy in some cases between the dome and trigone biopsy specimens. For example, in case 18, a paraplegic

Table 2 Résumé of clinical data of 20 paraplegics/tetraplegics in whom significant additional histopathological findings were seen either in the dome or in the trigone biopsy

<i>Patients</i>	<i>Sex</i>	<i>Date of birth</i>	<i>Date of onset</i>	<i>Level of lesion</i>
1	F	12-08-1924	1969	Multiple sclerosis. Incomplete tetraplegia
2	M	11-04-1926	1975	Transverse myelitis. Paraplegia T10
3	M	21-09-1971	18-12-1991	Traumatic tetraplegia C5
4	F	02-05-1965	26-06-1994	Traumatic incomplete perineal paraplegia
5	M	04-03-1953	24-11-1994	Traumatic tetraplegia C5
6	M	13-06-1938	06-02-1961	Traumatic paraplegia T9
7	M	23-12-1939	03-11-1993	Traumatic tetraplegia C5
8	M	06-02-1921	15-12-1962	Traumatic paraplegia L1
9	M	28-11-1937	11-04-1978	Traumatic paraplegia L3
10	F	25-06-1964	24-09-1983	Guillain-Barré syndrome tetraplegia C4
11	M	12-03-1928	06-09-1985	Traumatic tetraplegia C5
12	M	14-06-1950	09-10-1992	Traumatic paraplegia incomplete L4
13	M	07-07-1958	10-12-1991	Traumatic paraplegia L1
14	M	06-06-1973	29-07-1993	Traumatic tetraplegia C4-5
15	M	12-03-1950	23-05-1992	Traumatic paraplegia T12
16	M	11-09-1934	29-04-1967	Traumatic paraplegia T10
17	M	20-07-1945	07-09-1992	Traumatic tetraplegia C4-5
18	M	15-03-1969	since birth	Spina bifida with paraplegia L3
19	M	05-06-1976	since birth	Spina bifida with paraplegia T10
20	M	30-09-1931	24-01-1994	Traumatic tetraplegia C5-6

a

b

Figure 1 Microphotographs of mucosa of biopsy of the dome (a) in a 31-year-old tetraplegic (patient 10) on indwelling catheter showing urothelium involvement in interstitial cystitis whereas the mucosa in the biopsy of the trigone (b) shows squamous metaplasia with focal atypia. 5 micron paraffin section, haematoxylin and eosin stain, microscopical magnification 200×

patient practising self-intermittent catheterisation who also had a bladder calculus, EGF-R expression in bladder dome biopsy revealed positivity in the cytoplasm of some basal cells but the distribution was slightly patchy whereas in the biopsy specimen taken from the trigone of the urinary bladder, positivity was not detected in the urothelium with antibodies to epidermal growth factor receptor. Thus it seems clinically prudent to take at least two biopsies, one each from the trigone and the dome of the urinary bladder, even in the absence of any cystoscopically distinguishable abnormality in the bladder in those spinal cord injury patients who are at high risk for developing

bladder neoplasia because of either long standing indwelling urinary catheter drainage or recurrent chronic urinary infection associated with bladder calculi and/or urinary stasis.

Varying degrees of inflammatory reaction were observed in all the bladder biopsy specimens although it was more pronounced in some and well characterised in some others. Recently, immunohistochemical studies in inflammatory conditions and neoplasms of human urinary bladder have shown that expression of tenascin, an extracellular matrix glycoprotein that has considerable structural homology with fibronectin and epidermal growth factor correlates closely with the cellular

Figure 2 Microphotographs of biopsy of the dome (a) in a 71-year-old tetraplegic (patient 1) which shows follicular cystitis whereas the trigone biopsy (b) reveals squamous metaplasia. 5 micron paraffin section, haematoxylin and eosin stain, microscopical magnification a: 50 $\times$, b: 100 $\times$

Figure 3 Microphotographs of biopsies of the dome (a) in a 61-year-old paraplegic on penile condom drainage which shows mild dysplasia whereas the trigone biopsy (b) shows early adenomatoid metaplasia. 5 micron paraffin section, haematoxylin and eosin stain, microscopical magnification 200 $\times$

Figure 4 Microphotographs of biopsy of the dome (a) in a 19-year-old paraplegic which shows intestinal metaplasia whereas the trigone biopsy (b) shows features of extensive crypt metaplasia. 5 micron paraffin section, haematoxylin and eosin stain, microscopical magnification a: 100 $\times$, b: 200 $\times$

inflammatory response and that this may be the underlying mechanism for stromal remodelling.¹⁰ Myofibroblasts may be responsible for most tenascin synthesis, and prominent tenascin staining accompanies comparatively abundant and active inflammatory infiltrates and/or myofibroblastic proliferations. If a similar effect could be mediated to the epithelium, then alterations of the urothelial proliferation status may affect the propensity for bacterial colonisation and the development of biofilm. In view of the presently discussed role of biofilm in the vicious circle of chronic cystitis in the spinal cord injury patient, such a study has considerable clinical relevance as all of the 40 patients in the present study who had a neuropathic bladder showed evidence of one form or other of cystitis.

Acknowledgement

Ms Jacqueline Stevens, Regional Spinal Injuries Centre, Southport provided valuable administrative assistance in carrying out this study.

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