Urol Res (1984) 12:129–133

Urological Research

Cytomorphological and Histological Studies on the Urothelium During and After Chemoimmune Prophylaxis

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Accepted: October 30, 1983

Summary. During and after chemoimmune prophylaxis with i.v. cyclophosphamide (CTX) and both intravesical and systemic BCG-treatment, the bladder mucosa is prone to morphological changes which might resemble tumor recurrences. Therefore, morphological parameters which can discriminate between treatment effects and tumor recurrences are of interest. In a prospective study, routine cytology, determination of granulocytes, lymphocytes, and macrophages in the urine sediment as well as flow-cytophotometry (FCM) for DNA analysis were performed before, during, and after chemoimmune prophylaxis. In addition, bladder biopsies and all recurrent tumors were histologically analysed. Our results show that FCM is the best method for monitoring the bladder mucosa for recurrent tumors during treatment. After termination of BCG, it takes at least 4 months for cytological normalization to take place. Urine excretion of granulocytes, lymphocytes, and macrophages does not correlate with this process. Histological alterations during treatment are demonstrated; their normalization requires at least 3 months. In 10% of the patients chronic inflammatory lesions ("pseudotumors") develop.

Key words: Bladder cancer, chemoimmune prophylaxis, Pseudotumors, Histology, Flow-cytophotometry, Cytology.

Introduction

There is an increasing awareness of the beneficial effect of the intravesical BCG-application for prophylaxis in superficial bladder cancer [3, 5, 6, 8, 9, 12]. However, during and after these intravesical BCG instillations, alterations of the bladder mucosa take place which essentially consist of granulomatous and giant cell inflammation [2, 10, 11, 13] and marked dysplasia [13]. However, endoscopically these lesions are sometimes indistinguishable from pre-malignant or even cancerous lesions (Fig. 1). To our knowledge, neither the relationship between treatment and the appearance of suspicious lesions nor the efficacy of various morphological methods to monitor those patients on chemoimmune prophylaxis using cyclophosphamide and BCG (CTX/BCG) [3] have yet been examined. Therefore, in order to gain some insight into this complex matter, the following study was conducted.

Material and Methods

Since January 1978, we have performed chemoimmune prophylaxis after complete resection of superficial bladder tumors according to the schedule published previously [11]. After complete transurethral tumor resection the following morphological methods were sequentially employed in the absence of urinary tract infection or tumor recurrence. The time intervals were as indicated 1, 3, 5, 7, 9, 11, 15 or 19, and more than 22 weeks after TUR.

- Routine cytology: 366 sediments from voided urines were stained and examined according to Papanicolaou.
- Relative count of granulocytes, lymphocytes and macrophages: from 280 stained urine sediments the percentages of these cells were determined from at least 2,000 identifiable cells.
- Flow cytophotometry (FCM): DNA analysis of urothelial cells of 90 voided urine specimens was performed using our own modification [14].

Histology. In addition to these systematic examinations histological assessment of casual biopsies of the bladder mucosa during and after BCG instillations was performed. During the follow-up, all lesions which endoscopically appeared to be recurrent carcinomas of the bladder but histologically proved to be benign ("pseudotumors") were evaluated as to the pertinent urothelial and stromal alterations.

Results

After a single dose of cyclophosphamide, the percentage of normal findings (pap 1/2) slightly increases, whereas during the course of BCG instillations, an insignificant de-

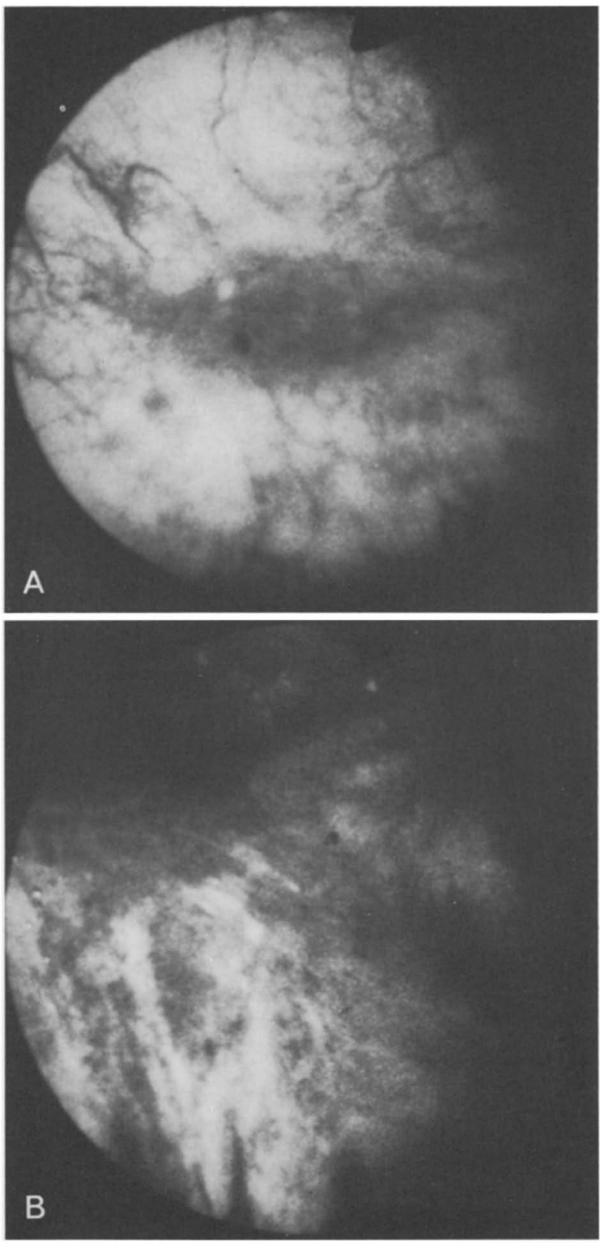

Fig. 1A, B. Endoscopic view of the bladder with **A** velvet-like spotty redness of the mucosa *during* treatment; **B** tumor-like lesion ("pseudotumor") 3 months *after* treatment

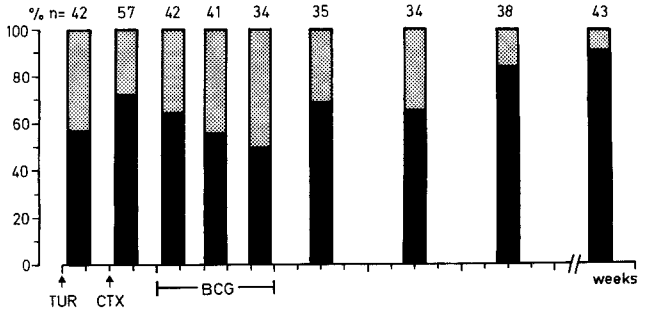

Fig. 2. Percentage of normal (pap 1/2) and abnormal (pap 3/4) cytological findings in relation to TUR, CTX- and BCG-treatment. ■: normal; ▨: abnormal

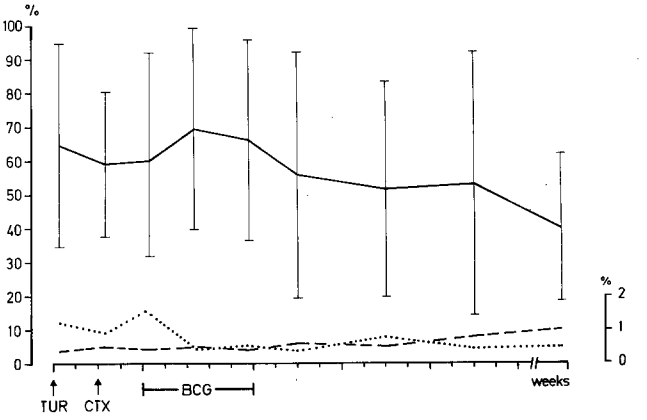

Fig. 3. Relative cell counts (%) of the urine sediment in relation to TUR, CTX- and BCG-treatment. ——: granulocytes; ·····: lymphocytes; – – –: macrophages

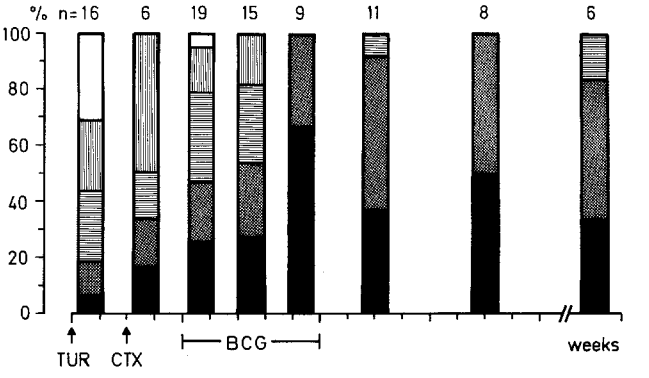

Fig. 4. FCM analysis of the urothelial cells in relation to TUR, CTX- and BCG-treatment.
□: clear aneuploidy
▥: slight aneuploidy } abnormal
▤: G_2M peak > 12% / euploidy
▨: G_2M peak 8–12% / euploidy } normal
■: regular DNA pattern

crease is noted. As late as 3 months after termination of this treatment, a clear tendency towards normalization is noticeable (Fig. 2).

Cell Counts. Relative counts of granulocytes show a small increase during BCG treatment followed by a gradual decrease. However, the standard deviations are very high so that no real shift can be ascertained. Both lymphocyte and macrophage excretions remain very low and are essentially unchanged during and after BCG treatment (Fig. 3).

Flow Cytophotometry (FCM). There is a constant increase of normal DNA patterns of the urothelial cells even during the BCG instillations. After termination of BCG treatment, the percentage of normal FCM findings remains essentially high (Fig. 4).

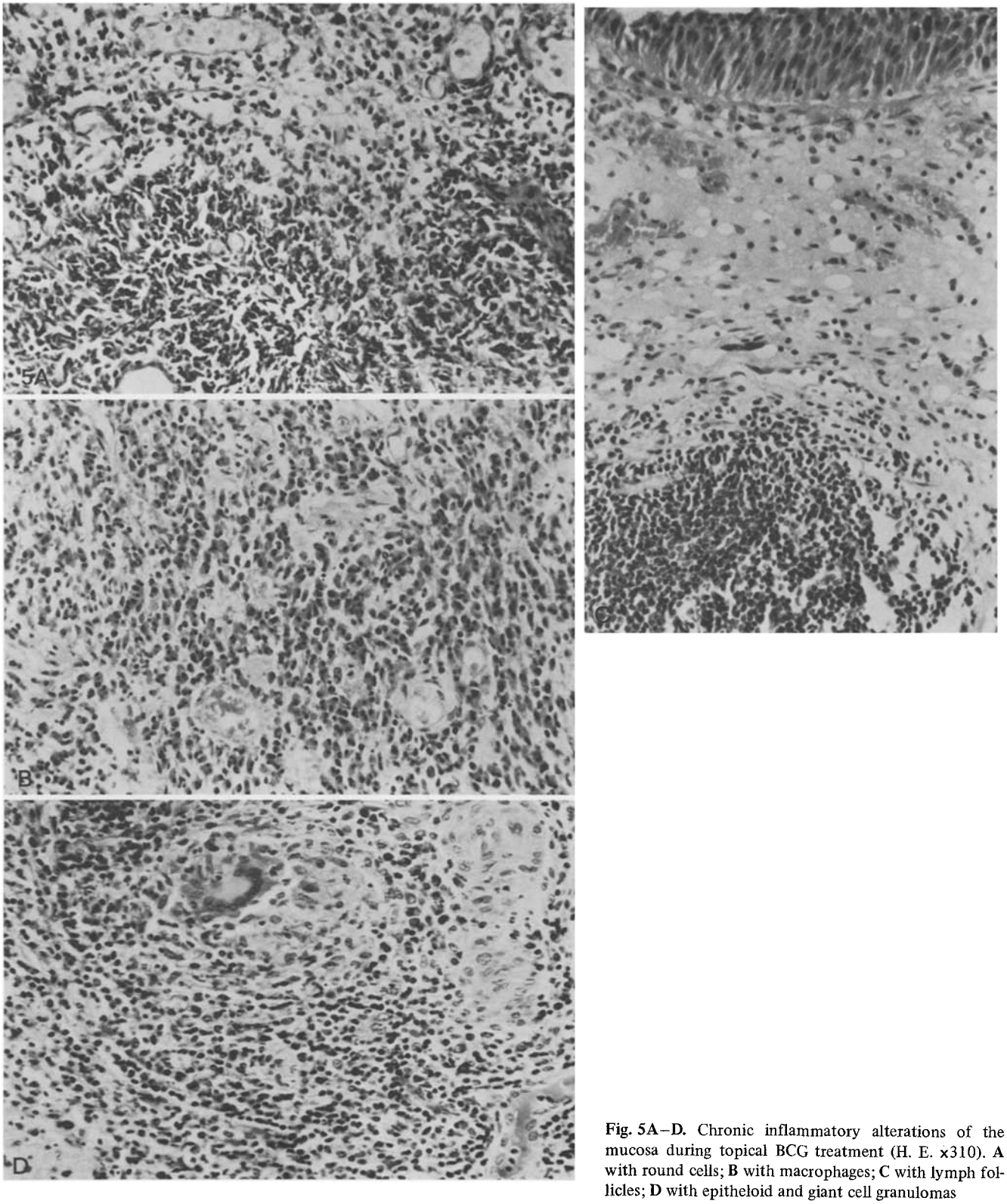

Fig. 5A–D. Chronic inflammatory alterations of the mucosa during topical BCG treatment (H. E. x310). **A** with round cells; **B** with macrophages; **C** with lymph follicles; **D** with epitheloid and giant cell granulomas

Histology. During BCG treatment, marked histological alterations of the mucosa take place, which 2–4 months after conclusion, return to normal (Figs. 5 and 6). Of 130 patients submitted to CTX/BCG treatment 13 developed "pseudotumors" [4]. Histological assessment of the resected material in these 13 cases revealed a predominantly chronic inflammatory pattern. Table 1 gives the details of the urothelial and stromal alterations.

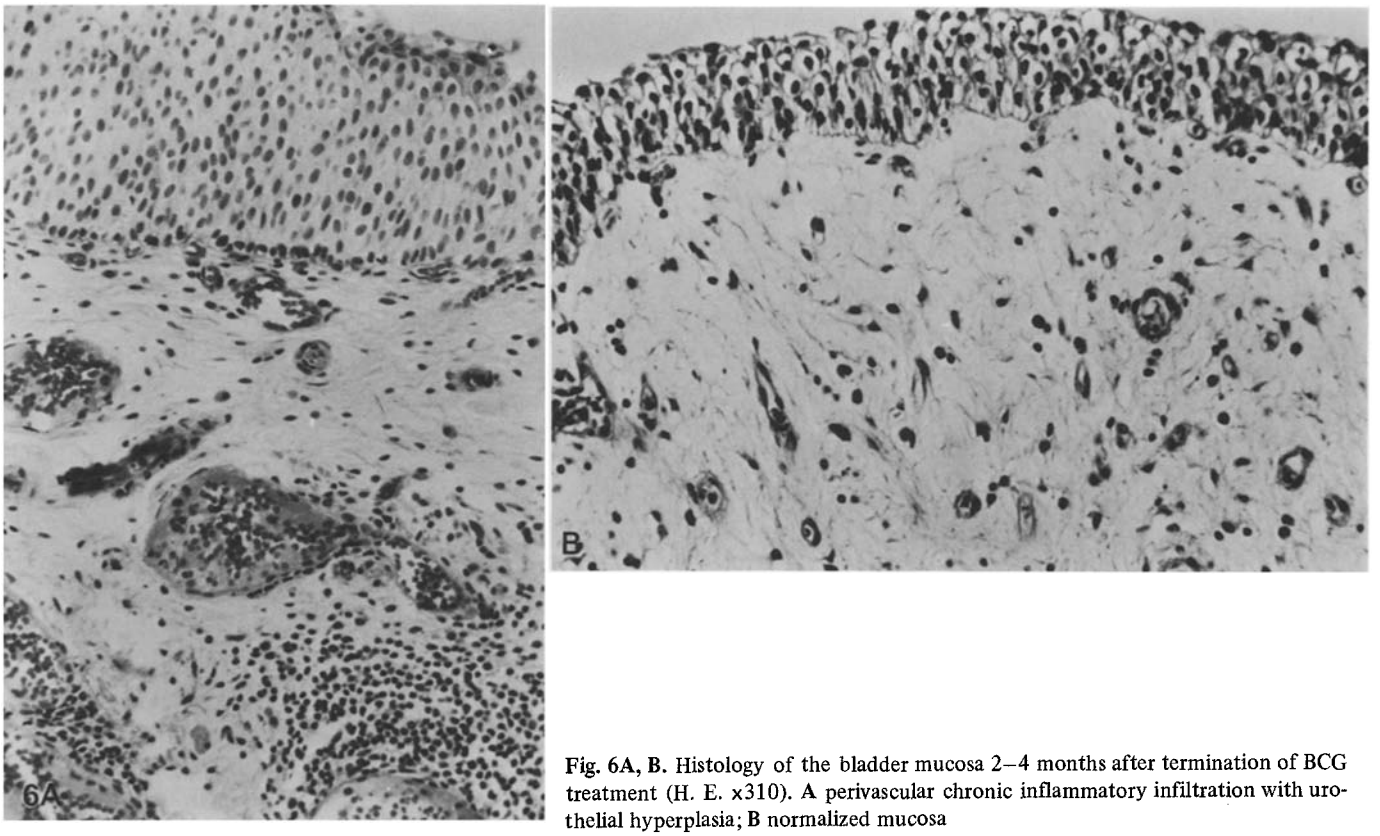

Fig. 6A, B. Histology of the bladder mucosa 2–4 months after termination of BCG treatment (H. E. x310). **A** perivascular chronic inflammatory infiltration with urothelial hyperplasia; **B** normalized mucosa

Table 1. Assessment of urothelial and stromal alterations in 13 patients with "pseudotumors"

urothelium			stroma			
papillary	flat	dysplasia I–III	lymphocytes plasma cells	lymphfollicle	giant cells	fibrosis
5	7	7	11	4	1	7

Discussion

During and after intravesical BCG treatment, the bladder mucosa is prone to inflammatory changes showing granulomatous lesions with giant cell, lymphocyte, macrophage, and plasma cell infiltrations together with urothelial dysplasia [2, 10, 11, 13]. All these alterations resolve later on [2]. Our results confirm these findings and prove in accordance with the endoscopic appearance of the bladder mucosa that the inflammatory changes resolve 2–4 months after termination of BCG treatment.

In our updated series of 130 patients with superficial tumors 13.5% of CTX/BCG treated patients develop recurrences and 10% "pseudotumors" [4]. It is most conspicuous that these "pseudotumors" are evenly distributed over the entire postoperative period without any peak incidence [4]. On histological examination they mainly show chronic inflammatory changes of the stroma with lymphocytes, plasma cells, fibrosis, lymph follicles, and giant cells in decreasing order. The urothelium may be papillary or flat with or without evidence of dysplasia (Table 1).

One question of practical interest relates to the diagnostic problem of how to distinguish between the inflammatory changes and true tumor recurrences. In our investigation three different morphological methods are sequentially employed during the course of CTX/BCG treatment. Of these methods, FCM analysis of the urothelial cells is most accurate for monitoring the bladder mucosa. In the absence of tumor recurrences this method shows normal results even during BCG instillations. The potential value of this method in this particular treatment modality has been shown by Klein et al. [7] on two patients. Cytology, on the other hand, proves to be accurate in approximately 50% during BCG treatment and in even higher percentages some months later. Conversely, determination of the relative percentage of excreted cells in the urine is of almost no value for monitoring the bladder mucosa.

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