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Current Concepts of the Aetiology, Pathogenesis and Pathology of Bladder Cancer

Gilbert H. Friedell

Departments of Pathology, St. Vincent Hospital and University of Massachusetts Medical School, Worcester, Massachusetts, USA

Summary. Attention is directed to the information currently available on the pathogenesis of human bladder cancer. The continuum between carcinoma, carcinoma-in-situ and other epithelial abnormalities is noted. Pre-neoplastic lesions are defined as irreversible but not necessarily progressive, and a possible morphologic marker for pre-neoplasia seen with scanning electron microscopy is described.

Key words: Bladder - Pathogenesis - Pre-neoplasia - Scanning Electron Microscopy.

It is actually known what causes some bladder cancers. Certain chemicals such as beta-naphthylamine and para-aminodiphenyl are clearly responsible for some cases of bladder cancer in man. This has provided a starting point for research, and allowed some steps to be taken to prevent bladder cancer.

In many parts of the world the manufacture and use of these and other compounds identified as bladder carcinogens is either restricted or no longer allowed. At the same time advanced technology now permits the detection of trace quantities of such powerful bladder carcinogens in the occupational or general environment, or in the urine of those suspected of exposure to these agents. It is becoming evident, however, that weak bladder carcinogens are recognised less easily and are more difficult to deal with effectively. Moreover it has not yet been determined whether human bladder cancer may be due to exposure to high doses of multiple weak chemical carcinogens, or to a low dose of a strong carcinogen together with or followed by a high dose of one more weak chemical carcinogen. Finally, research on the aetiology of bladder cancer has tended to concern itself with either chemical or biological agents, rather than combinations. The latter approach is being further investigated, and may be very helpful in both identifying aetiological factors and elucidating mechanisms of their action.

PATHOLOGY

In the United States, the vast majority of bladder cancers are transitional cell carcinomas with a small number of squamous cell carcinomas, adenocarcinomas, and a few so-called mixed carcinomas in which two or more of the three morphologic patterns may be present (6). Tumour grading appears to have some prognostic importance, particularly for transitional cell carcinomas. Using a three-grade system, it has been reported recently that approximately 6% of Grade 1 transitional cell carcinomas, 52% of Grade 2 tumours, and 82% of Grade 3 tumours were invasive (6).

Transitional cell carcinomas that are Grade 1 and at the same time both papillary and non-invasive give the greatest difficulty in classification. Very few cases will develop metastases from Grade 1 transitional cell carcinomas of the bladder, and death due to such tumours is an extremely rare occurrence. It is in this group of cases that the greatest difficulty arises in predicting biological behavior from histological examination.

PATHOGENESIS

Regardless of aetiology, the pathogenesis of human urinary bladder cancer appears to be comparable in many ways to carcinoma of

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the uterine cervix, the bronchus or the oral cavity, although certain obvious points of difference immediately come to mind. Bladder cancers are predominantly of transitional cell type, whereas the majority of tumours at the other sites mentioned are squamous, and there are many more papillary tumours in the bladder than are seen at the other sites. The similarity, on the other hand, lies in the fact that at all of the sites mentioned - including the bladder - invasive carcinoma appears in many cases to arise within, or in association with, an area of carcinoma-in-situ, and this in turn appears to develop within a larger field of atypical epithelium. This point has been particularly well illustrated for bladder cancer in giant sections of the urinary bladder prepared from radical cystectomy specimens (1, 2, 17, 18).

Another means of demonstrating the geographic relationship between carcinoma, carcinoma-in-situ and areas of lesser epithelial abnormalities is by mapping the histological patterns seen in the usual, postage-stamp size, tissue sections from cystectomy specimens in which all of the epithelial surface of the bladder has been submitted for microscopic examination (14). Recently Farrow and his colleagues have reported the results of studying cases in this way (4, 5).

There seems to be general agreement that in many cases of bladder cancer the invasive tumour is associated with non-invasive - usually flat - carcinoma of the same histological type, as well as extensive areas of epithelial hyperplasia and dysplasia. On the other hand, as pointed out by Soto et al. (18), this is not always true, and some 20 % of their 45 cases studied in giant sections had no significant epithelial abnormality associated with invasive cancer.

In addition to establishing the fact that transitional cell or squamous carcinomas of the bladder have a spatial relationship to carcinoma-in-situ and to epithelial hyperplasia, studies by Melamed (16), Koss (15) and their co-workers and by others (2, 5, 9) have demonstrated a temporal relationship between epithelial hyperplasia, dysplasia, carcinoma-in-situ and invasive transitional cell or squamous tumours. Particularly since the advent of exfoliative cytology and its use as a case finding method in high risk populations, it has been possible to follow patients for several years as their bladder epithelium reveals this progression from hyperplastic and dysplastic epithelium through 'in-situ' to invasive carcinoma. Thus, in bladder cancer as in carcinoma of the cervix there is a clearly established relationship - both in space and in time - between carcinoma-in-situ and invasive carcinoma (7).

Pre-neoplastic Lesion

The identification of pre-neoplastic lesions is currently a matter of great interest to many pathologists. A pre-neoplastic lesion may be defined as a proliferation of epithelial cells with characteristic but non-neoplastic histological features, associated in space or time with the development of 'in-situ' or invasive carcinoma of the same histological type. The constituent cells are atypical, but individually and collectively do not look like malignant cells. The lesion, if not entirely removed by biopsy, might persist in this form or it might progress to 'in-situ' and/or invasive carcinoma (8). Part of the nomenclature problem is that in discussing the fate of the lesion - whether or not it will be irreversible and/or progress to carcinoma - it is implied that the outcome is a function of the epithelium itself. The possibility or probability of "rejection" of the hyperplastic epithelium by the host is usually ignored.

In theory the term "pre-neoplastic lesions" should be applied only to those in which the epithelial change is irreversible but not necessarily progressive, while the term "neoplastic" would be reserved for those lesions which were not only irreversible but progressive. The problem, of course, is that this distinction cannot be made for human patients at present using morphological criteria and our catalogue of "pre-neoplastic lesions" contains many lesions which look alike but which are benign and not destined to become malignant.

A marker of some sort is needed which would indicate that the abnormal epithelium had entered an irreversible state, i.e., the pre-neoplastic state as defined above. Such a marker has been noted in an experimental animal model (10, 11). Because recent studies suggest that this same marker might have similar significance for humans, the relevant information from these investigations will be briefly reviewed.

An Experimental Model for Bladder Carcinogenesis

For the past ten years we have been defining the bladder tumour model in which the carcinogen N-(4-(5-nitro-2-furyl)-2-thiazolyl) formamide (FANFT) is fed to Fischer rats in the diet. In an early study, Tiltman and Friedell (19) noted that feeding this compound for more than 10 weeks resulted in the presence

of bladder tumours in all animals. On the other hand, if animals were fed the compound for 4 weeks the hyperplasia of bladder epithelium which was present when the carcinogen feeding was discontinued regressed completely after several weeks of control diet. Further studies of the reversibility or irreversibility of lesions induced by FANFT feeding were then done in our laboratory (3, 10, 11). Groups of animals were fed FANFT at a concentration of 0.2% in the diet for 2, 4, 6, 8, 10, 12, 14, 16 and 20 weeks, after which each group was placed on a control diet and sacrificed at intervals up to 84 weeks. Complete autopsies were done. The bladders were examined by light, scanning (SEM) and transmission electron microscopy.

Moderate to marked epithelial hyperplasia, occasionally with a papillary or nodular pattern, was evident at the end of the feeding period in animals from the experimental groups fed FANFT for 4, 6, 8 and 10 weeks. The hyperplasia in groups fed FANFT for 4 and 6 weeks then regressed completely by 20 weeks and the bladder epithelium appeared normal by light and SEM at 52 and 84 weeks. The "8 week" animals had persisting hyperplasia at 20 weeks, and tumours at 52 weeks. The "10 week" animals had tumours by 20 weeks. We found that at the end of the initial feeding periods, cells at the surface of hyperplastic lesions from animals fed FANFT for 8 or 10 weeks were covered by numerous pleomorphic microvilli when viewed with SEM, although with light microscopy the hyperplasias at 6, 8 and 10 weeks all looked alike. On the other hand, cells comprising the hyperplastic lesions in animals fed FANFT for 4 or 6 weeks had on their luminal and intercellular surfaces only those regular microvilli normally seen on normal basal and intermediate cells. By 20 weeks the luminal cells in these "4 week" or "6 week" animals appeared normal, with uniform microridges on their surfaces - the appearance of bladder epithelium in control animals.

Irreversible Epithelial Hyperplasia

Pleomorphic microvilli in this experimental model seem to indicate at least an irreversible epithelial hyperplasia, i.e., a pre-neoplastic lesion as previously defined. Their presence might also be an indicator of progression, as well as irreversibility, but at the moment it is thought of as a marker for pre-neoplasia. It has also been possible to identify this marker with SEM on the surface of exfoliated rat bladder epithelial cells. The details of the method have been published previously (12). Collected urine samples are filtered through a sintered silver membrane and the trapped cells are then processed for SEM. The presence of pleomorphic microvilli on the exfoliated cells is readily identified.

Cellular Characteristics in Human Bladder Carcinoma

Applying the same technique for processing exfoliated bladder epithelial cells to urine samples from patients with bladder cancer pleomorphic microvilli are readily identified (13). Examination of biopsy material by SEM indicates that luminal cells in a human bladder are not generally covered by normal microridges; instead fairly uniform microvilli are commonly seen. However, it would appear that pleomorphic microvilli are not normally seen on epithelial cells lining the bladder lumen, nor are such pleomorphic microvilli seen between intermediate cells or between basal and intermediate cells. Pleomorphic microvilli are present on bladder tumour cells in preparations of tissue or exfoliated cells. Whether or not the presence of pleomorphic microvilli on these cells will have the same import as it does in our experimental model remains to be seen. However, these findings are encouraging and in time it may be possible to identify individuals from high risk populations in whom appropriate therapeutic intervention will be able to prevent the appearance of bladder cancer in the form in which it is commonly seen today.

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Gilbert H. Friedell, M.D.
Department of Pathology
St. Vincent Hospital and
University of Massachusetts Medical School
Worcester, MA
USA