Virchows Archiv A Pathol Anat (1989) 414:273–277

Virchows Archiv A
Pathological Anatomy and Histopathology

Human chorionic gonadotrophin expression and histological findings as predictors of response to radiotherapy in carcinoma of the bladder

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Summary. A retrospective analysis of the prognostic value of pretreatment histology and expression of human chorionic gonadotrophin (B-hCG) was carried out in 100 invasive (T2/T3) transitional cell carcinomas of the bladder treated in a uniform manner. After transurethral resection of the tumour, all patients received a course of radical radiotherapy, with salvage cystectomy for those who failed to respond. Forty-nine of 100 patients responded to radiation; thus 51 did not. Forty-seven of 60 (78%) patients whose tumours contained areas of squamous differentiation and 22 of 29 (76%) of tumours staining positively for HCG failed to respond to radiotherapy. Twenty-two of 23 (96%) patients with tumours that had both these features did not respond to radiotherapy. The other histological features studied (grade of tumour, necrosis, inflammation, vascular invasion, and growth pattern) appeared unrelated to each other or to clinical outcome.

Key words: Transitional cell carcinoma – Bladder – Squamous metaplasia – Human chorionic gonadotrophin – Radiotherapy – Prognosis

Introduction

The overall prognosis of patients with invasive (UICC stage T2/T3) transitional cell carcinoma (TCC) of the bladder remains disappointing whatever treatment they are offered. The effectiveness of radical radiotherapy and elective cystectomy has been shown to be similar to the combination of radiotherapy and elective cystectomy. There appear to be, however, two tumour populations, approximately one half being radiosensitive and the other radioresistant. This is of crucial importance since regression of the primary tumour after radiotherapy is the most important prognostic factor in determining survival (Blandy et al. 1980; Jenkins et al. 1988). Several previous studies have attempted to identify poor prognostic groups using particular histological features, but most of this work has been performed on cystectomy specimens, with small series or with heterogeneous tumour populations (Jewett et al. 1964; Pomerance 1972; Slack et al. 1980).

The beta subunit of human chorionic gonadotrophin, (B-hCG) has been recognised in a wide range of extragonadal tumours (Braunstein et al. 1973), including those of the urothelium (Shah et al. 1987; Rodenburg et al. 1985). B-hCG has also been suggested as a biological marker of prognostic significance in carcinoma of the colon (Campo et al. 1987).

We have reviewed a series of 100 cases of invasive TCC for the presence of B-hCG and related this to the histological features and clinical response.

Materials and methods

The series comprised 100 patients with invasive (UICC stage T2/T3) transitional cell carcinoma of the bladder, treated at the London Hospital between 1980 and 1986. All patients were treated by transurethral resection of the tumour followed by megavoltage irradiation to the bladder only at a dose of 5000–5500 cGy in 20 fractions over 4 weeks, as described by Hope-Stone (1986). The response to radiotherapy was assessed at cystoscopy and biopsy at three and six months after treatment.

The histological sections of the original, pretreatment tumours stained with haematoxylin and eosin were reviewed independently by three pathologists unaware of the clinical outcome. Between 1 and 7 blocks of tissue were available in each case, (mean 2.6). The tissue had been fixed in 10% formol saline and embedded in paraffin wax. The slides were assessed

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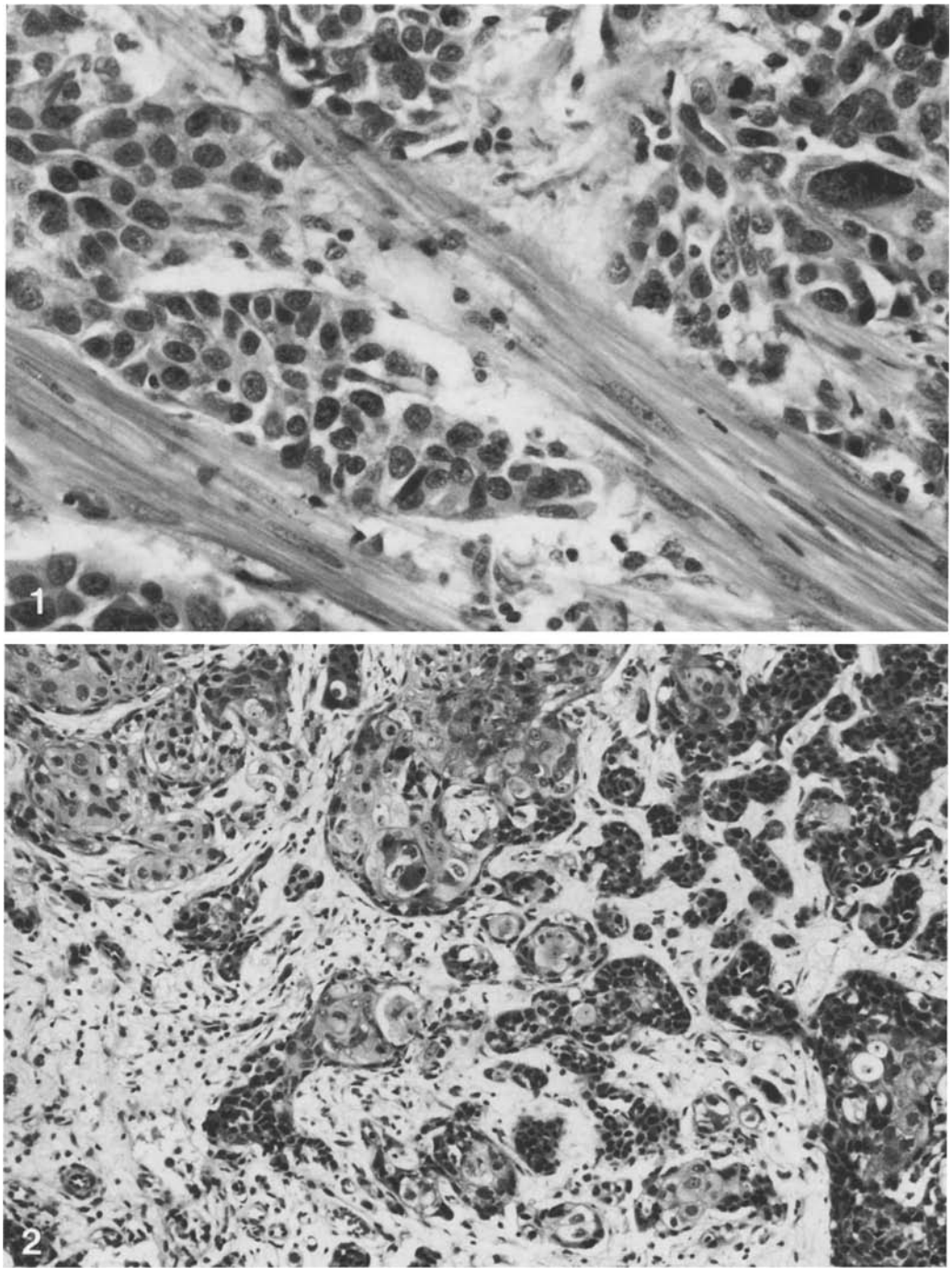
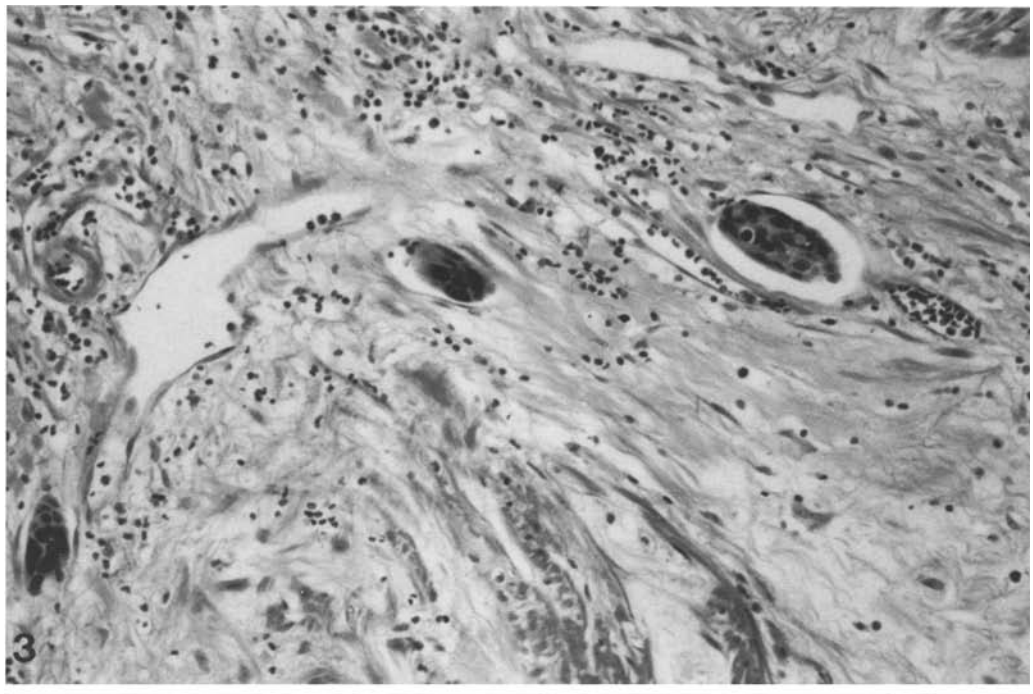


Fig. 1. Poorly differentiated transitional cell carcinoma invading muscle of the bladder wall. (HE ×240)

Fig. 2. Invasive transitional cell carcinoma showing areas of squamous metaplasia. (HE ×225)

for the degree (graded 0, +, + +, or + + +) and type (acute, chronic or mixed) of inflammatory cell infiltrate, the presence of necrosis, papillary or solid growth pattern, vascular invasion and the presence of squamous metaplasia within the tumour (Figs. 1, 2, 3). The grade of the tumour was also noted, in accordance with the UICC system (G1, G2, G3).

The tissue was stained using an indirect immunoperoxidase technique for B-hCG. The sections were dewaxed through xylene to alcohol, placed in 0.3% hydrogen peroxide in methanol for 15 min at room temperature to block endogenous peroxidases, washed with TRIS buffer at a pH of 7.6 then incubated with normal swine serum (diluted 1:5) for ten min. The excess was then discarded and the sections overlaid with rabbit anti-B-hCG in a 1:25 dilution in TRIS buffer for 20 min. After wash-



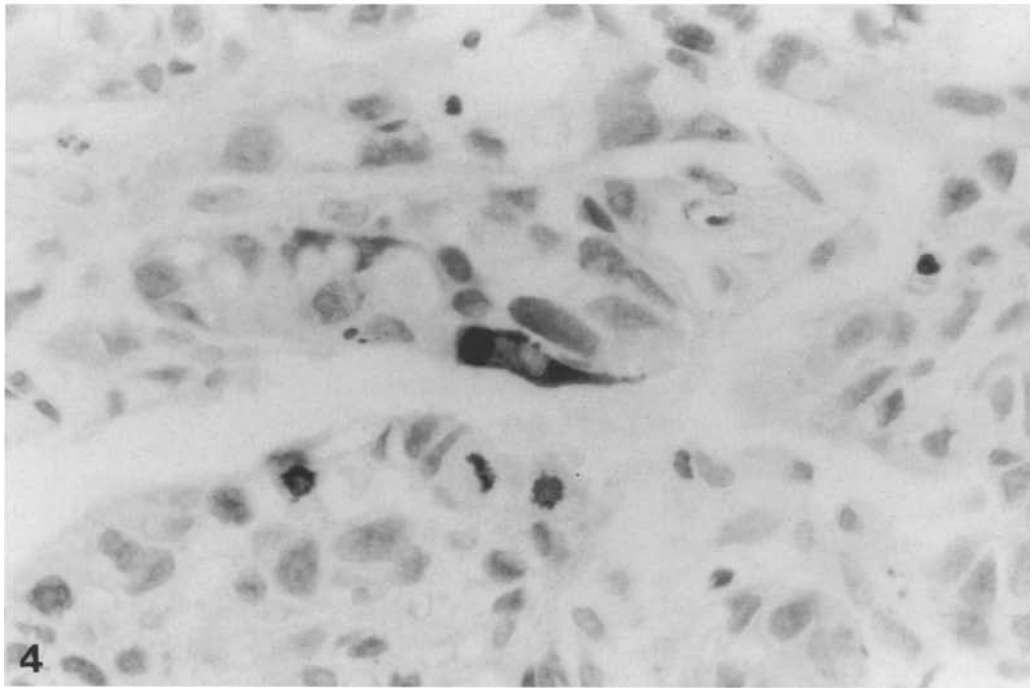


Fig. 3. Vascular invasion by transitional cell carcinoma. (HE ×225)

Fig. 4. B-hCG positive transitional cell carcinoma cells. (Immunoperoxidase ×240)

ing, the sections were covered with peroxidase-conjugated swine antirabbit immunoglobulin, (diluted 1:20) and incubated for 20 min. The peroxidase complex was visualised using 3:3′diaminobenzidine and hydrogen peroxidase. Sections were counterstained with Mayer's solution, dehydrated through graded alcohols, cleared in xylene and mounted in synthetic medium. The usual controls were applied (Crocker and Smith 1984).

Results were analysed using the Chi squared test and a multivariate analysis.

Results

The mean age of patients was 68.3 years (range 33–85), 78 were male and 22 female (male:female = 3.5:1). Ninety-two tumours were classified as G3 and the remaining 8 as G2. Sixty tumours showed areas of squamous metaplasia and 29 stained positively for B-hCG. B-hCG staining was

Table 1. Correlation of various histological features

G2+G3 tumours		Response to radiotherapy		Squamous metaplasia		B-hCG expression		Necrosis		Vessel invasion		Growth pattern	
		+	−	+	−	+	−	+	−	+	−	P	S
Response to radiotherapy	+	49		13	36	7	42	25	24	22	27	22	27
	−		51	47	4	22	29	28	23	27	24	23	28
Squamous metaplasia	+	13	47	60		23	37	33	27	35	25	26	34
	−	36	4		40	6	34	20	20	14	26	19	21
B-hCG expression	+	7	22	23	6	29		14	15	18	11	11	18
	−	42	29	37	34		71	39	32	31	40	34	37
Necrosis	+	25	28	33	20	14	39	53		23	30	17	36
	−	24	23	27	20	15	32		47	26	21	28	19
Vessel invasion	+	22	27	35	14	18	31	23	26	49		21	28
	−	27	24	25	26	11	40	30	21		51	24	27
Growth pattern	P	22	23	26	19	11	34	17	28	21	24	45	
	S	27	28	34	21	18	37	36	19	28	27		55

P = Papillary surface, S = Solid

usually patchily distributed, with staining seen often only in small clusters of cells at the invading edge of the tumour (Fig. 4). Necrosis was present in 53 tumours. Forty-five showed a papillary surface and 55 were solid. Small vessel invasion was seen in 49 cases. Of the 93 tumours showing an inflammatory cell infiltrate, 75 showed mild, 17 moderate and 1 marked changes. Two tumours showed acute inflammation, 46 chronic and 45 a mixed picture.

Forty-nine tumours responded to radiotherapy, with no residual tumour apparent at cystoscopy and biopsy (Table 1).

Forty-seven of 60 (78%) patients whose tumours contained areas of squamous differentiation and 22 of 29 (76%) of those which expressed B-hCG failed to respond to radiotherapy (Chi squared test, $p < 0.005$). Twenty-three of 29 (79%) tumours which stained for B-hCG also contained areas of squamous metaplasia.

A multivariate analysis showed no significant correlation between the presence of squamous metaplasia, B-hCG expression and the other histological features.

Twenty-two of 23 (96%) tumours with squamous metaplasia that also expressed B-hCG failed to respond to irradiation, whereas only 3 of 34 (4%) lacking both features showed no response.

Discussion

Until now, reports of B-hCG secretion in bladder tumours have been largely sporadic and anecdotal and none have related it to prognosis. We have demonstrated B-hCG expression in 29% of our cases and this proportion is similar to other reports (Shah et al. 1986; Collino et al. 1986). Of the tumours that expressed B-hCG, 76% failed to respond to radiotherapy. This group also contained a large proportion of cases with areas of squamous metaplasia, (23 of 29–79%).

B-hCG expression was not related to other histological features such as necrosis or inflammation suggesting that this may be a specific phenotypic variant of transitional cell carcinoma, and one which accompanies radioresistance.

The importance of predicting radiosensitivity of a tumour before therapy has been emphasised (Boileau et al. 1980). Campo et al. found that B-hCG staining in colonic carcinoma tended to be present in more advanced lesions and hence ones with a poorer prognosis. Our results suggest that although only 29 of our cases stained positively for B-hCG, this expression may indicate radioresistance and thus poor prognosis, since no response was seen in 22 of these (76%). Moreover, when it is found in association with squamous metaplasia, the rate of failure of response is extremely high (22 of 23 cases −96%).

We conclude that B-hCG expression in invasive transitional cell carcinoma of the bladder may be used as a strong independent predictor of radioresistance. When B-hCG is found in conjunction with squamous metaplasia there is an even higher likelihood of lack of response to radiotherapy and therefore other treatment modalities should be considered.

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Received August 30, 1988 / Accepted December 2, 1988