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Prognostic Significance of Peritumoural Inflammation in Invasive Urothelial Bladder Carcinoma

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Summary. Peritumoural inflammation consisting of lymphocytes, plasma cells and lymph follicles is present in two thirds of invasive urothelial bladder carcinomas. This type of inflammation is significantly rarer in advanced tumour stages (P3, P4) and its presence is a favourable prognostic factor. The mean survival time in patients with this type of inflammation is 26.1 months compared to only 14.8 months in patients without. All other forms of inflammation e. g. eosinophilic or polymorphonuclear leukocytes have no relation with prognosis. The significant prognostic value of lympho-plasmocytic inflammation may be considered as local expression of immunological host resistance.

Key words: Urinary bladder carcinoma - Peritumoural inflammation - Prognosis.

The significance of host resistance with respect to the genesis and spread of malignant tumours is impressively illustrated by the increased incidence of malignancies in children suffering from congenital immune deficiency syndromes (15) in renal transplant recipients (24) and by cases showing spontaneous tumour regression (13). Cellular and humoral immunological reactions against tumour-associated antigens have been demonstrated in recent years for a variety of tumours including carcinoma of the urinary bladder (1, 2, 7, 8, 9, 18, 19, 22, 23). Since the majority of investigations have been restricted to in-vitro studies, the present study was carried out to determine whether or not the morphological evidence of peritumoural inflammation (PI) is an expression of host resistance to urinary bladder carcinoma and whether this reaction is of prognostic significance. Numerous studies have been devoted to these questions for carcinomas of other organs (3, 4, 5, 6, 10, 21, 26), but little attention has been paid to urinary bladder carcinomas (25).

MATERIAL AND METHODS

The material presented in this paper was obtained from 107 patients undergoing transurethral resection for invasive urothelial bladder carcinoma from 1966-1972. Specimens obtained from the first resection were classified according to the following criteria: Tumour type (solid/papillary), tumour stage (P 1, P 2, P 3 and P 4) and grade of differentiation (I = highly differentiated to IV = anaplastic).

Peritumoural inflammation (polymorphonuclear leukocytes (PL), eosinophilic leukocytes (EL), lymphocytes (LC), plasma cells (PC) and lymph follicles (LY) was evaluated semi-quantitatively and scored from 0 (absent or minimal) to +++ (extensive).

The statistical evaluation of the material encompassed the morphological parameters as well as patient's age and sex, incidence of tumour recurrence, survival time or time of follow up (minimum 12 months). The results were evaluated for statistical significance with the U-test according to Mann Whitney and the chi-square-test. The survival rate was determined by the method of Cutler and Ederer (11).

RESULTS

The results are summarised in table 1. In 29% of the tumours, no PI was found (Fig. 1 A). In 50.5% a mixed infiltration consisting of

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Table 1

Tumour type	Tumour stage	Differentiation grade	LC, PC 0	+	++	+++	Ly 0	+	++	+++	LC, PC, Ly 0	+-+++	EL 0	+	++	+++	PL 0	+	++	+++
Solid type n = 52 ♂ 45; ♀ 7	P 1 n = 9	I, II n = 2	1	-	-	1	1	1	-	-	1	1	1	1	-	-	1	1	-	-
		III, IV n = 7	2	5	-	-	4	2	1	-	2	5	4	2	1	-	4	2	1	-
Age: <50: 6 (yrs) <60: 10 <70: 21 <80: 12 >80: 3	P 2 n = 33	I, II n = 2	1	1	-	-	-	1	1	-	1	1	2	-	-	-	2	-	-	-
		III, IV n = 31	12	10	6	3	20	5	4	2	8	23	17	3	6	5	21	2	5	3
	P 3, 4 n = 10	I, II n = 2	2	-	-	-	2	-	-	-	2	-	2	-	-	-	1	-	1	-
		III, IV n = 8	6	1	-	1	5	-	-	3	5	3	6	1	1	-	8	-	-	-
Papillary type n = 55 ♂ 42; ♀ 13	P 1 n = 26	I, II n = 20	8	5	3	4	16	3	1	-	7	13	12	4	3	1	16	4	-	-
		III, IV n = 6	2	3	1	-	3	2	1	-	1	5	1	3	2	-	4	2	-	-
Age: <50: 5 (yrs) <60: 10 <70: 22 <80: 16 >80: 2	P 2 n = 28 + P 3, 4 n = 1	I, II n = 8	5	2	-	1	6	1	-	1	3	5	6	2	-	-	7	1	-	-
		III, IV n = 20+1	9	4	4	4	14	2	4	1	7	14	9	7	4	1	12	5	2	2
Total	-	-	48	31	14	14	71	17	12	7	37	70	60	23	17	7	76	17	9	5

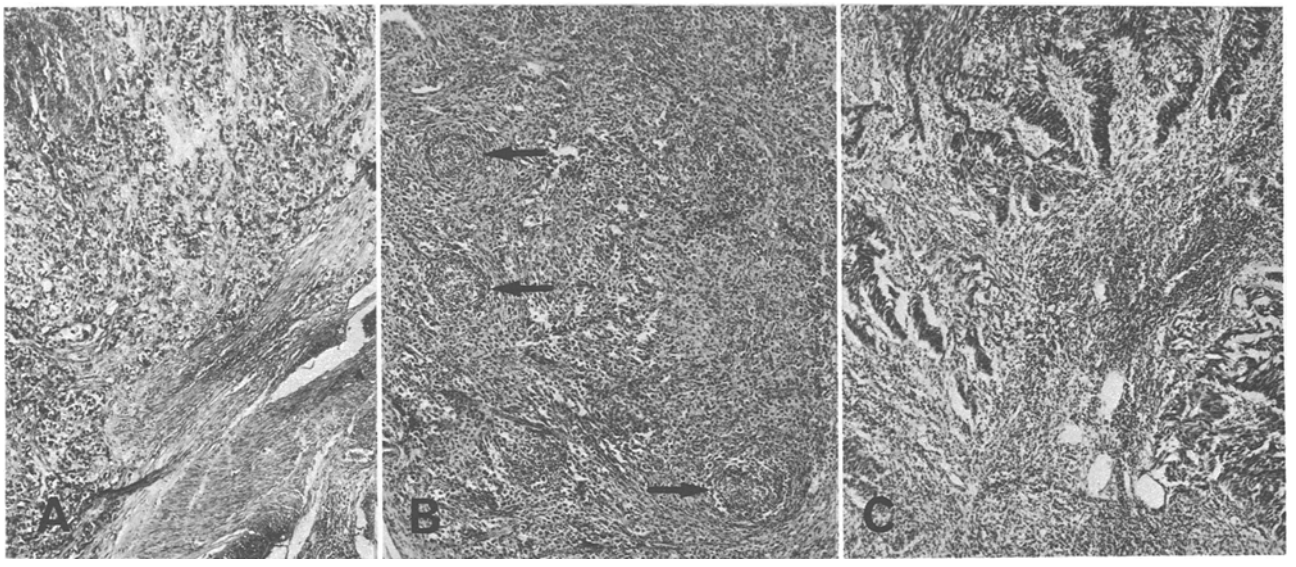

Fig. 1. Different forms of peritumoural inflammation in urinary bladder carcinoma. (A) No inflammation. (B) Numerous lymph follicles (⟶) and pronounced diffuse permeation of tumour by lymphocytes and lymphocyte clusters. (C) Diffuse inflammation consisting of lymphocytes and plasma cells at the plane of infiltration. HE stain (x 48)

Table 2

	Survival time		Test-statistics
	⩽12 mo	>12 mo	(Chi-square-test)
	n = 56		
No inflammation	12	11	ns
Inflammation present	12	21	
No eosinophils or polymorphonuclear leukocytes	16	19	ns
Eosinophils and/or polymorphonuclear leukocytes present	9	12	
No lymphocytes/ plasma cells and lymph follicles	15	10	$p < 0.025$
Lymphocytes / plasma cells and/or lymph follicles present	9	22	

ns = not significant

Table 3

	Lymphocytes, plasma cells, lymph follicles		
	Present	Absent	Test-statistics
Total time of follow up Mean/SD (months) n = 107	36.6 (SD 27.9)	25.0 (SD 27.0)	$p < 0.0028$ (U-Test)
Survival time Mean/SD (months) n = 56	26.1 (SD 22.5)	14.8 (SD 14.4	$p < 0.043$ (U-Test)
5 yrs survival[a] rate (%) SE (%)	51 SE 8	29 SE 8	$p < 0.05$ (t-Test)[c]
Effective sample size (n)	32	29	
5 yrs survival[b] rate (%) SE (%)	52 SE 8	28 SE 15	$p < 0.1$ (t-Test)[c]
Effective sample size (n)	39	9	

[a] including stage P 3, 4

[b] excluding stage P 3, 4

[c] based on the approximation of standard deviation (SD) from standard error (SE) and hypothetical effective sample size (11)

lymphocytes, plasma cells, lymph follicles and polymorphonuclear leukocytes was present. A pure lymphocyte/plasma cell PI occurred in 10.2% of all cases and lymph follicles only in 8.4% (Fig. 1B). Eosinophilic leukocytes were seen in 1.8%. A pure polymorphonuclear leukocytic PI was not encountered, while polymorphonuclear leukocytes were generally found associated with focal tumour necrosis. EL, PC, LC and LY often formed a forder at the depth of infiltration (Fig. 1C).

Between tumour type, stage, degree of differentiation, incidence of recurrence, age and sex on the one hand and the type of PI on the other, statistically (chi-square-test) only 2 significant ($P < 0.05$) findings were obtained:

1. EL are encountered more frequently in women.
2. PI consisting of LC, PC and LY is encountered more rarely in cases of advanced carcinoma (P 3, P 4) than in earlier stages (P 1 and P 2; see Table 1).

However, no significant difference emerged between P 1 and P 2.

Between the type of PI and the survival time or total time of follow up, there is only a significant correlation for LC, PC and LY type of PI (Table 2). 52% of patients with this kind of PI demonstrated a 5-year survival rate compared to only 29% of those in whom it was absent. Even when advanced cases are included (P 3 and P 4) the 5-years survival rate of patients with PI was 51% and for those without only 28% (Table 3). The total time of follow up is significantly longer when lymphocytes, plasma cells and lymph-follicles are present in the peritumoural inflammation than in their absence (Table 3). The same holds true for the survival time which is about 26 months in patients with this type of inflammation and only about 15 months in those without (Table 3).

DISCUSSION

Three statements can be made on the basis of these studies:

1. One third of the urinary bladder carcinoma investigated had no LC, - PC, - LY-type PI.
2. LC, - PC, - LY-type PI is significantly rarer in advanced stages of carcinoma (P 3, P 4) than in earlier stages (P 1 and P 2).
3. The presence of an LC, - PC, - LY-type of PI is prognostically more favourable than its absence. This is also true if advanced cases (P 3, P 4) are not considered. Other types of inflammation (PL, EL) have no relationship to survival rate.

In a previous study which also included non-infiltrating carcinomas (25) essentially consistent findings were also noted. An LC, - PC, - LY-type of PI was present in two thirds of the cases and the prognosis was intimately associated with the extent of this type of PI.

On the basis of these findings, we propose that the LC, - PC, - LY-type of PI represents an independent prognostic factor, since this type of PI does not correlate with other prognostic factors such as tumour type, grade of differentiation and stage.

The LC, - PC, - LY-type of PI may be explained in two ways:

1. It is the result of non-specific reaction or an accompanying bacterial infection (27) or ....
2. It is the expression of a local immunological host resistance against the tumour tissue.

We feel that the first proposition can be discarded since in advanced stages (P 3 and P 4) the LC, - PC, - LY-type PI is less common than in early stages when just the contrary might be expected due to tumour necrosis with superficial ulceration. We therefore submit that the prognostically favourable influence of an LC, - PC, - LY-type of PI is not only the consequence of unspecific inflammatory resistence, but rather the expression of local immunological host resistence. In most cases the PI consists of a mixed infiltrate of LC, PC and LY which, in the local setting, strongly suggests a predominantly humoral immunological reaction. This suggestion is supported by the fact that immunoglobulins can be demonstrated in urinary bladder carcinoma (20). Nontheless - as evidenced by in-vitro studies - cellular rather than humoral immunoresponses are said to be of greater significance. In fact, humoral responses have been reported to promote tumour growth by enhancing antibodies (18). This assumption is contradicted not only by the prognostically favourable influence of LC, - PC, - LY-type PI, but also by recent in-vitro studies which have indicated complement-dependent cytotoxic antibodies (7) and cell mediated antibody-dependent cytotoxicity (16).

The reason why infiltrating carcinomas (tumour stages P 3 and P 4) demonstrate PI less commonly, is not understood. It may be that the malignancy destroys the PI during its rapid growth or that there are tumours which from the very onset do not induce PI due to deficient host immune capability, deficient profiling of tumour-associated antigens or formation of enhancing antibodies (12, 14, 18).

The significance of PI remains unexplained (4). Simultaneous morphological and in-vitro studies may lead to a better understanding. PI in urinary bladder carcinoma merits consideration in studies of the immune status of cancer patients.

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