Lymphocytic Infiltration in Bladder Cancer*

A PRELIMINARY REPORT

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SUMMARY

A preliminary, random sample study has been made of 34 cases of carcinoma of the bladder, correlating the degree of lymphoid reaction to the tumour, as seen in the original biopsy specimen before treatment, with the grading, staging and subsequent follow-up. These findings were consistent with those of Sarma, in that a significant statistical correlation could be demonstrated between a low-grade tumour and presence of lymphoid reaction ($P = 0{,}005$), and the absence of same in high-grade lesions ($P = 0{,}005$). This effect was not so obvious in tumour staging, but appeared significant in comparing stage B1 lesions, with or without lymphoid reaction. The influence on local recurrence and distant metastases also appeared significant with tumour control in the presence of lymphoid reaction ($P = 0{,}07$), and conversely recurrences and/or metastases in the absence thereof ($P = 0{,}07$).

S. Afr. Med. J., **47**, 192 (1973).

Lymphocytic infiltration of various malignant neoplasms has long been recognized, and its significance was attributed to either infection or post-irradiation change, or both. Tumours in a hollow viscus such as the urinary bladder are especially prone to secondary infection, and are usually irradiated at some stage during their management. However, lymphocytic infiltration of malignant bladder neoplasms can exist purely on an immunological basis, due to the presence of tumour-specific antigens as shown by Bubenik *et al.*[1,2]

Sarma[3] demonstrated the presence of adventitious lymphoid tissues and classified the degree of lymphoid reaction, ranging from odd collections of cells to well-defined follicles crowding the tumour in 73% of a large series of cases (Table I and Figs 1 - 4). He showed a significant inverse correlation between the quantitative degree of lymphocytic infiltration and the malignant nature, invasiveness and progression, and ultimate prognosis of the bladder lesion.

TABLE I. SARMA'S CLASSIFICATION OF LYMPHOID REACTION

1. Negative (−): Complete absence of collections of lymphoid tissue (Fig. 1).
2. Slight (+): Odd collections of lymphoid cells, indefinite follicles, or the inconstant appearance of a definite follicle (Fig. 2).
3. Moderate (++): Appearance of definite follicles at regular intervals (Fig. 3).
4. Marked (+++): Extensive formation of well-organized and giant follicles (Fig. 4).

*Date received: 7 August 1972.

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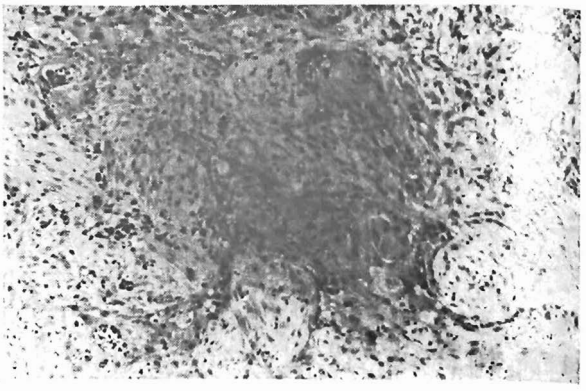

Fig. 1. Photomicrograph (× 40) of anaplastic tumour showing absence of lymphoid reaction (−).

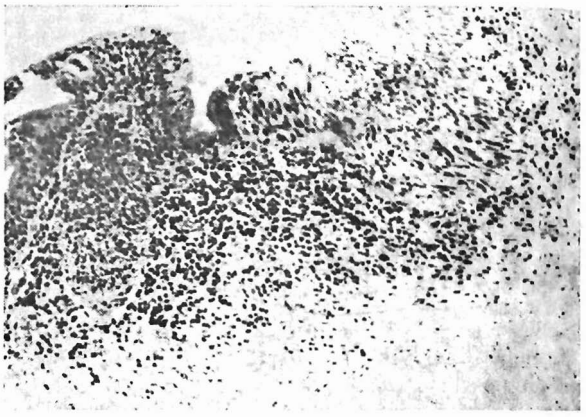

Fig. 2. Photomicrograph (× 40) of well-differentiated tumour showing slight lymphoid reaction (+).

The following is a preliminary report of a similar study made in the Urological Division of the Johannesburg General Hospital.

MATERIAL AND METHOD

To date, 128 patients with bladder carcinoma are documented in the Bladder Cancer Clinic, during the period January 1958—October 1971.

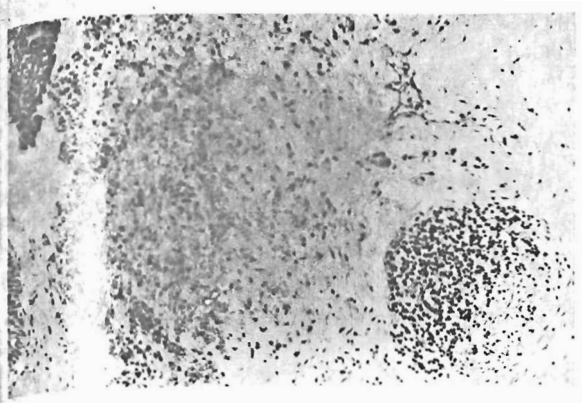

Fig. 3. Photomicrograph (× 40) of well-differentiated tumour showing moderate lymphoid reaction with definite nodular lymphoid aggregation (++).

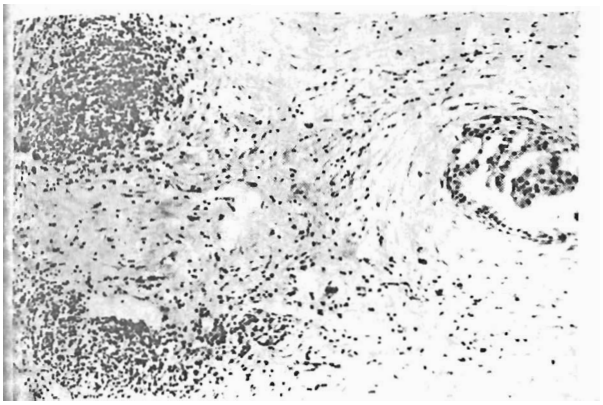

Fig. 4. Photomicrograph (× 40) of adenocarcinoma of the fundus of the bladder with marked lymphoid reaction and regular nodular lymphoid aggregates (+++).

A sample of 34 of these cases was selected at random from the Cardex of the clinic, and subjected to a double-blind histological reassessment of the original tumour material, with consideration as to cell type, Broder's grading, histological staging as regards depth of invasion (Jewett's classification, 1952), and the presence and degree of lymphoid reaction, according to Sarma's classification (Tables II and III).

TABLE II. GRADING DISTRIBUTION AT PRESENTATION, AND DEGREE OF LYMPHOID REACTION

Lymphoid reaction	Grade of lesion		Totals
	I and II	III and IV	
—	0	7	7
+, ++, +++	17	10	27
Totals	17	17	34

TABLE III. CORRELATION OF STAGE OF TUMOUR INVASION WITH LYMPHOID REACTION

Lymphoid reaction	Stage of invasion (Jewett)						Totals
	O	A	B1	B2	C	D	
—	—	1	3	2	1	—	7
+	1	9	4	—	—	2	16
++	2	2	1	—	—	—	5
+++	—	1	3	—	2	—	6
Totals	3	13	11	2	3	2	34

These patients were followed-up over a period extending from 6 months to 7 years, and reassessed for evidence of control of tumour, local recurrence, and lymphatic or distant metastases by clinical evaluation, histology of the biopsy specimens obtained by transurethral resection, and, in certain instances, laparotomy and post-mortem examination. These findings are again compared with the degree of lymphoid reaction shown in the original tumour analysis (Tables IV and V).

TABLE IV. LOCAL RECURRENCES RELATED TO DEGREE OF LYMPHOID REACTION

Lymphoid reaction	Local recurrence		Totals
	Present	Absent	
—	7	0	7
+, ++, +++	17	10	27
Totals	24	10	34

TABLE V. DISTANT METASTASES RELATED TO DEGREE OF LYMPHOID REACTION

Lymphoid reaction	Distant metastases		Totals
	Present	Absent	
—	5	2	7
+, ++, +++	9	18	27
Totals	14	20	34

RESULTS

The histological assessments as to degree of lymphoid reaction and grade of differentiation of tumour, are compared in Table II. Seven tumours showed no lymphoid reaction, and 27 varying degrees from + to +++. Of those with no lymphoid reaction, all 7 were high-grade lesions, whereas of those showing lymphoid reaction, 17 were low-grade tumours.

The histological assessments as to stage of tumour invasion and degree of lymphoid reaction, are compared in Table III. Three stage B1 lesions showed no lymphoid

reaction. All 3 died within 12 months. Two of these died from their disease, and the third from an intercurrent coronary thrombosis. These were all high-grade lesions (grades III and IV). This is compared with 3 stage B1 lesions, which showed a marked lymphoid reaction (+++). One died at 10 years, and a second at 1 year from their disease, and the third is still alive at 2 years. All 3 were low-grade lesions (grade II). Two patients with stage C lesion showed a marked lymphoid reaction (+++). Both died of disease within 12 months and both were high-grade lesions (grades III and IV).

Cystoscopic evidence of local recurrence is compared with degree of lymphoid reaction in the original biopsy specimen in Table IV. All 7 cases in which there was no lymphoid reaction demonstrated local recurrence. Of 27 cases showing lymphoid reaction, there was no demonstrable local recurrence in 10.

Clinical, operative or necropsy evidence of distant metastases is related to the degree of lymphoid reaction in the original biopsy in Table V. Of 7 cases showing no lymphoid reaction, distant metastases were present in 5. Of 27 cases showing lymphoid reaction, distant metastases were present in only 9.

DISCUSSION

Although the series here reported is considerably smaller, the findings of this preliminary study are consistent with those of Sarma,[3] and appear to be statistically significant. It is generally accepted that it is the inherent nature of the tumour that ultimately determines prognosis, irrespective of the treatment given.

Well-differentiated tumours appear to be associated with lymphoid reaction, and poorly-differentiated tumours with an absence of such reaction. There is a high correlation between the presence of a low-grade lesion (grades I and II) and lymphoid reaction ($P = 0{,}005$). Similarly, there is a high correlation between presence of a high-grade lesion (grades III and IV) and absence of lymphoid reaction ($P = 0{,}005$) (Table II).

No apparent significant beneficial relationship is demonstrated between degree of lymphoid reaction, and stage of tumour invasion (Table III). This is inherent in the small number of cases in the study. However, it may prove significant that all 3 stage B1 lesions without lymphoid reaction were high-grade tumours with a poor prognosis, relative to the 3 stage B1 lesions with marked lymphoid reaction which were low-grade tumours, carrying a seemingly better prognosis.

Lymphoid reaction appears to influence local recurrence (Table IV). Local recurrence is commoner in the absence of lymphoid reaction ($P = 0{,}07$). Similarly, freedom from local recurrence is correlated with lymphoid reaction ($P = 0{,}07$).

The occurrence of distant metastases is significantly affected by lymphoid reaction to the primary tumour (Table V), as distant metastases appear to be more common in the absence of a lymphoid reaction ($P = 0{,}07$). Similarly, absence of distant metastases is correlated with lymphoid reaction ($P = 0{,}07$).

Obviously, in order to confirm the conclusions in Sarma's study of positive correlation between significant lymphoid reaction and low incidence of invasion, and over-all good prognosis and survival, a much more extensive series will have to be undertaken.

We should like to thank Dr J. J. Rippey and Mrs I. Massel, respectively of the Schools of Pathology and Statistics of the University of the Witwatersrand, Johannesburg, for valuable advice in the preparation of this article; and the Medical Superintendent of the Johannesburg General Hospital for permission to publish.

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2. *Idem* (1970): *Ibid.*, 5, 310.
3. Sarma, K. P. (1970): J. Urol., **104**, 843.