

Tumour-associated eosinophilia in the bladder

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SUMMARY Tumour eosinophilia is an uncommon but striking phenomenon which has been found in many tumours, mostly of large cell type or squamous differentiation. The incidence, appearance and importance of tumour eosinophilia in the bladder are described. Eosinophilia is commoner in deeply invasive tumours and in tumours showing squamous metaplasia. Transitional cell carcinomas with eosinophilia have a better prognosis than those without, but this improvement is not seen in squamous cell carcinomas of the bladder. When eosinophilia is found on superficial biopsies of a bladder tumour, the possibility of muscle invasion should be considered.

In recent studies of tumour eosinophilia^{1,2} it was found that in the skin and mucous membranes the phenomenon of massive tumour-associated tissue eosinophilia (TATE) appeared to be related to the histological differentiation and cell type of the tumours in which it occurred. As at many other sites³ the tumours with TATE were large cell, poorly keratinising squamous cell carcinomas. To continue the study and to test this hypothesis further, transitional cell carcinomas of the bladder were reviewed, with particular reference to those tumours in which squamous metaplasia was present.

Material and methods

The cases diagnosed as transitional cell carcinoma and squamous cell carcinoma of the bladder in the department of histopathology at St Thomas's Hospital Medical School between 1968 and 1982 were reviewed. An assessment of the presence and extent of squamous differentiation within the tumours was made, based on the demonstration of keratin formation or intercellular bridges. Tumours with squamous metaplasia of 25% or more of the total tissue area on the available sections were considered to have appreciable squamous change.

The number of eosinophils within the epithelial islands of tumour and in the immediately adjacent stroma was counted. Those in which there were more than 100 eosinophils per high power field (0.159 mm² on the microscopes used) in ten high power fields were considered to have massive TATE. The pattern of the eosinophil infiltrate and its extent within the bladder wall in these cases was

noted.

The clinical details of the patients with massive TATE were retrieved from the case notes. Information on the duration, clinical stage, method of treatment and subsequent course of the tumours was recorded. The staging system of the International Union Against Cancer⁴ was applied. Survival figures on some of the cystectomy cases were kindly provided by the South Thames Cancer Registry.

Since schistosomal infection of the bladder might induce both squamous metaplasia and an eosinophil infiltrate, transitional cell carcinomas from patients who had been born in or who were known to have visited countries in which schistosomiasis was endemic were excluded from the study. Also excluded were tumours which were obviously ulcerated or necrotic, as these conditions may also excite tissue eosinophilia.

Results

The number of cases reviewed and the proportion with TATE are shown in Table 1. The figure for biopsy specimens does not include those on whom cystectomy was subsequently performed. The figures for cases of transitional cell carcinoma with squamous differentiation include cases previously diagnosed as squamous cell carcinoma of the bladder.

Proportionately more cases of TATE were found in the cystectomy specimens than in the biopsy specimens. In tumours with squamous change, the incidence of TATE was about four times higher than in the tumours without; this was true in both biopsy and cystectomy specimens. Since there were squamous areas on the surface of the tumours well away

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Table 1 *Cases of bladder carcinoma reviewed*

	Total cases	Cases with massive TATE
Biopsy specimens		
Pure TCC	1192	21 (1.8%)
TCC with squamous metaplasia	62	4 (6.5%)
Cystectomy specimens		
Pure TCC	41	5 (12.2%)
TCC with squamous metaplasia	10	6 (60.0%)
All cases	1305	36 (2.76%)

TATE = tumour associated tissue eosinophilia; TCC = transitional cell carcinoma.

from the dense eosinophil infiltrate in the deep lamina propria and muscularis, the appearances did not suggest that the squamous metaplasia was induced in these cases by the eosinophilia itself.

There was no relation between the histological grades of the transitional cell carcinomas and the presence within them of TATE. Irrespective of squamous change, the transitional cell element in most tumours was moderately differentiated. The squamous areas were non-keratinising and moderately differentiated in both eosinophilic and non-eosinophilic tumours.

In the cystectomy specimens with TATE the tumour cells extended deep into the muscularis and in some cases through into the perivesical adipose tissue. Small islands and strands of malignant cells were surrounded by an infiltrate of eosinophils, which was most dense at the level of the muscularis and became sparser towards the mucosal surface. As described in other eosinophilic carcinomas, the eosinophils extended between malignant cells and surrounded small groups of them. No eosinophil microabscesses were seen. Muscle necrosis was not a feature, though there was obvious fibre damage with evidence of regeneration adjacent to the invasive tumour cells. This was present to the same degree and in the same distribution in tumours without TATE, and therefore appeared to be related to the tumour rather than to the eosinophil infiltrate.

Table 2 *Survival of cystectomy cases*

	Mean survival		
	All cystectomy cases	Cystectomy cases without massive TATE	Cystectomy cases with massive TATE
All cases	2.36	2.07	3.10
Cases with pure TCC	2.13	1.82	3.61
Cases with TCC with squamous differentiation	2.76	2.80	2.71

TATE = tumour associated tissue eosinophilia; TCC = transitional cell carcinoma.

The ages of the patients in this series ranged from 30 to 96 years, with a mean of 54 years. The tumours at all stages were about twice as common in men. The presence of TATE was not related to age or sex, nor to the symptoms or length of history before presentation. There were no cystoscopic features to distinguish these tumours. One patient had had eosinophilic cystitis diagnosed on biopsy. Follow up cystoscopy nine months later showed a moderately differentiated papillary transitional cell carcinoma with no invasion of the lamina propria. None of the other cases had had histological evidence of bladder eosinophilia before the tumour was diagnosed.

The clinical stage of the biopsy specimens could not be confidently assessed because of the possibility of sampling error. More than half, however, were well or moderately differentiated papillary tumours with no evidence of muscle invasion, and the overall stage for the group would almost certainly be I or II. The cystectomy cases were all stage III or IV; these showed a greater proportion of tumours with squamous metaplasia than the biopsy cases, which reflects the surgical practice in managing such tumours at St Thomas's Hospital.

The mortality figures for the cystectomy cases are given in Table 2. The mean survival figures are for patients now deceased; in all of the categories in Table 2 there are patients still alive, though none for longer than four years after diagnosis.

Circulating eosinophilia was found concurrently with TATE in seven cases. The eosinophil count ranged from 0.658 to 2.916 × 10⁹/μl (normal 0.44 × 10⁹/μl). In four patients the eosinophil count returned to normal on convalescence, and no subsequent eosinophilia developed. In the other three patients blood eosinophilia persisted. All three died within four months of cystectomy with disseminated malignancy.

Discussion

Eosinophil infiltration in malignant tumours has been found in a variety of tissues.^{3,5} It does not appear to be related to the site or aetiology of the tumours, nor to an idiosyncrasy of the patients in whom it occurs.¹ Most tumours with TATE are large cell, non-keratinising, moderately differentiated squamous cell carcinomas.

In this series tissue eosinophilia was present with a greater frequency in tumours with squamous metaplasia. In these, the incidence of TATE was about five times higher than in tumours without, and this was true for both biopsy and cystectomy cases. This suggests that if the pathogenesis of the infiltrate is related to a tumour associated eosinophilotactic or

eosinophilopoietic factor, as has been proposed,⁶⁻⁹ malignant squamous cells are more likely to secrete this than malignant transitional cells. On the other hand, four of the 10 cystectomy cases with squamous metaplasia did not have eosinophilia, indicating that TATE is not simply a feature of the metaplasia itself.

The percentage of tumours with TATE was higher in the cystectomy group than in the biopsy cases, irrespective of the presence of squamous metaplasia. It would appear, therefore, that in tumours where TATE is found there is a greater likelihood that deep invasion has occurred with involvement of the muscularis.

In an earlier report of eosinophils in bladder carcinoma, Tiltman in Cape Town¹⁰ found a heavy eosinophil infiltrate in 7.1% of biopsy specimens. The reason for the prevalence of eosinophilia being over twice as high in South Africa as in Great Britain is not clear. Schistosomiasis as a causative agent was excluded as far as possible in the African series, but it is conceivable that in some case this might have been present but inapparent. A more likely explanation might be that presentation to surgery is later in Africa and the tumours might have progressed to a more advanced stage of invasion.

There are histological similarities between the tumours with TATE and the lesions of eosinophilic cystitis. Considerable eosinophil infiltration with particular concentration near areas of muscle fibre damage may be seen in both conditions.¹¹ In eosinophilic cystitis the cause of the muscle damage is not known, but in the malignancies reported here it was the direct result of tumour invasions. Fibrosis of the lamina propria and muscularis may be present in both eosinophilic cystitis and carcinoma; in our cases the features of this were more suggestive of a desmoplastic reaction around the tumour than of healed inflammation. Eosinophilia was not present in areas of the bladder not affected by tumour. It is difficult to determine whether eosinophilic cystitis is a disease entirely distinct from eosinophilia with malignancy, or whether the two conditions overlap. Previously described cases of eosinophilic cystitis have been associated with malignancy, and such was the case in the single instance in this series. It is not known whether eosinophilia in the bladder is a forerunner of malignancy, predisposes to malignancy, or develops as a reaction to it.

The mean survival for all cystectomies was higher

in those with TATE than in those without. It may be seen from Table 2 that the somewhat better prognosis is confined to patients with pure transitional cell tumours; eosinophilia does not influence the prognosis of cases with squamous differentiation.

Thus it appears that the finding of eosinophilia in bladder carcinoma is commoner in tumours with squamous differentiation and in tumours at a late stage of invasion. There is a better prognosis in pure transitional cell carcinoma with tissue eosinophilia. The finding of TATE on a biopsy specimen may be suggestive of invasive malignancy which has not been sampled, and in such cases rebiopsy or careful follow up might be considered.

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