Tumour-associated eosinophilia: a review

DAVID LOWE, JOHANNA JORIZZO, MSR HUTT

From the Department of Histopathology, St Thomas's Hospital Medical School, London SE1 7EH

SUMMARY In a recent study of cervical carcinoma, 13 cases with a marked eosinophil infiltrate around the tumour were found. The histological appearance of the tumours was distinctive and suggested a specific response, similar to the lymphocyte infiltration in medullary carcinoma of the breast and seminoma. A review of published reports shows that tumour-associated tissue eosinophilia (TATE) and tumour-associated blood eosinophilia (TABE) may be seen in tumours of different histological types from different anatomical sites, and may occur together or separately. Tumours with TATE alone appear to have a better prognosis than those without, while TABE is associated with tumour spread and a poor prognosis.

The idea that a tumour may induce a protective reaction in its host antedated by many years the modern concepts of immune surveillance of tumours.¹ The association between proliferating tumour cells and a lymphocyte infiltrate has been recognised for over 50 years.^{2,3} In a recent review Ioachim⁴ emphasises the distinctive patterns of cellular reaction to different histological types of neoplasm and underlines the need to study lymphocytes and plasma cells at the tumour site, rather than in the peripheral blood. He does not, however, mention eosinophils as a stromal response.

During a recent study of 460 cases of cervical carcinoma from Malawi⁵ an assessment was made of cellular infiltration of the stroma within and adjacent to the tumour. In 13 cases (3%) there was a very marked tissue eosinophilia with over 100 eosinophils per high power field of stroma. Eosinophils were seen both around and within the tumour, often separating the cells into small groups (Figs. 1-3). In some areas the tumour cells appeared to have lost cohesion, with individual cells lying separately encircled by eosinophils. The presence of eosinophils was not associated with tumour necrosis or with ulceration.

The histological features of this group were characteristic, and appeared to be distinct from cases with minor degrees of tissue eosinophilia (37% of the total), while in 60% there were no eosinophils in the 10 fields examined. In all but one case the tumours with marked tissue eosinophilia were large cell non-keratinising squamous carcinomas, which was the

most common histological variant in the whole series. No significant eosinophil infiltrate was seen in the endometrium or myometrium of these patients. There was no relation between tissue eosinophilia in these tumours and schistosomal infection, though this is common in Malawi.

An analysis of histological material from patients with cervical cancer diagnosed at St Thomas's Hospital revealed 2% of squamous cell carcinomas with an identical picture of tissue eosinophilia. This appearance was also seen in 1% of penile carcinomas from Malawi but was not seen in 100 biopsies of oesophageal carcinoma. These studies suggest that tumour-associated tissue eosinophilia (TATE) is a very specific reaction to certain tumours. In view of recent advances in our knowledge of eosinophil function in health and disease, in particular of its possible role as a killer cell, it was decided to review the literature on eosinophilia with tumours.

Eosinophils have been recognised for over 100 years. They were first described by Wharton Jones⁶ in 1846 as "coarse granule cells" and later by Ehrlich⁷ as eosinophils. Since that time there have been a large number of reports describing TATE, both with and without concomitant tumour-associated blood eosinophilia (TABE). These two aspects of eosinophilia with tumours often show disparity⁸⁻¹⁰ and may represent quite different host responses.

Tumour-associated tissue eosinophilia

There appears to be little in common between the types of tumour which show a marked TATE, save that they are almost all tumours at a body surface.

Fig. 1 Large cell non-keratinising carcinoma of the cervix showing TATE. Haematoxylin and eosin, formalin-fixed paraffin embedded tissue $\times 32$.

Fig. 2 The same tumour as in Fig. 1 There is infiltration of the tumour and its stroma by large numbers of eosinophils, which separate the tumour cells into small groups. Haematoxylin and eosin, formalin-fixed paraffin embedded tissue $\times 128$.

Fig. 3 Semithin section of resin-embedded tissue showing well granulated eosinophils infiltrating between tumour cells $\times 128$.

CARCINOMA OF THE CERVIX

There are a large number of reports of TATE in cervical carcinoma.¹⁰⁻²⁹ The descriptions in these publications suggest that throughout the world a small percentage of these tumours, usually of the large cell non-keratinising type, will show this phenomenon and that it may be regarded as a distinct histopathological entity. There is no evidence to suggest that TATE in cervical cancer is linked to any other specific disease and it may or may not be associated with TABE. Eosinophils in large numbers are not seen in the normal cervix or in non-specific chronic cervicitis in adults²⁷ though one case of a marked eosinophil infiltrate in a neonatal cervix is described.³⁰ An increase in uterine eosinophils can be induced in mice using oestradiol,^{31 32} and oestrogen receptors have been demonstrated on eosinophil cytoplasmic membranes.³³ However, eosinophils were not seen in our cases in tissue from the endometrium, nor in those reported by Bjersing and Borglin.²⁷ It appears probable that the TATE is a specific response to particular tumours and is unrelated to hormonal factors.

CARCINOMA OF THE LUNG

Certain types of lung carcinomas have been associated with TATE.³⁴⁻⁴⁰ The majority of these have been large cell undifferentiated carcinomas. Tissue eosinophilia has not been reported in oat cell carcinoma. Wasserman *et al*³⁸ have isolated an eosinophilotactic factor from a large cell undifferentiated carcinoma of the lung; this substance was functionally similar to the naturally occurring eosinophil chemotactic factor of anaphylaxis ECF-A, which suggests that the attraction of a marked eosinophil infiltrate may be attributable to the tumour cells themselves. This view is supported by reports of eosinophils being found in large numbers in malignant pleural effusions,^{41 42} where they may form rosettes around tumour cells,⁴² and by a similar production of an eosinophilotactic factor by Hodgkin's cells in tissue culture.⁴³

OTHER TUMOURS WITH TATE

Tissue eosinophilia has been described in squamous carcinomas of the vagina,²⁴ penis,^{44 45} skin,^{20 46} and nasopharynx;⁴⁷ in adenocarcinomas of the stomach,^{9 20 26} large bowel^{9 20 26 48} and uterine body;^{28 44} and in transitional cell carcinoma of the bladder.⁴⁴ There is little in common between these sites of occurrence, except that they are all at a body surface. There was no apparent relation between the eosinophilia and ulceration.

Other than in Hodgkin's disease, TATE is rarely seen in sarcomas, but has been reported in other forms of malignant lymphoma⁴⁹⁻⁵¹ and in malignant

fibrous histiocytoma.⁵²

Metastatic tumour in lymph nodes and liver may show TATE.^{45 53 54} We have seen a case of nasopharyngeal carcinoma in cervical lymph nodes which showed very marked tissue eosinophilia. TATE in metastases may or may not be associated with eosinophilia in the primary tumour.

TATE AND PROGNOSIS

The prognosis of patients showing TATE without blood eosinophils is generally considered to be good.^{9 13 17 23 46 54} In our series of cervical carcinoma, follow-up was not possible but it is of interest that in 11 of the 12 cases in which extent of spread was recorded, there was only local disease. Tumour eosinophilia before treatment is thought to be a favourable prognostic sign^{14 16} in cervical carcinoma, and adenocarcinoma of the stomach with TATE has a better prognosis than tumours with the same clinical stage but with no eosinophilia.⁹

Experimental evidence is in keeping with this: the growth of implanted tumours in mice is inhibited if the implantation site has tissue eosinophilia⁵⁵⁻⁵⁷ and damage to mammalian tumour cells by eosinophils has been reported.^{58 59} It is doubtful whether phagocytosis of tumour cells by eosinophils is important in man⁶⁰ and phagocytosis was not observed in our cases. On the other hand, mammalian cells are damaged by high molecular weight cationic proteins⁶¹ and it is suggested that similar damage is caused by eosinophil major basic protein.⁵⁹ The use of antieosinophil serum⁶² may allow in vivo studies of tumour eosinophilia, though specific antibodies have yet to be developed.⁶⁰

Tumour-associated blood eosinophilia

Blood eosinophilia is described in the same range of tumours as tissue eosinophilia.^{9 10 22 28 29 34-36 39 48 49 63-84} It is also seen in carcinomas of the kidney,^{85 86} adrenal,⁴⁸ thyroid,^{87 88} liver,⁸⁹ gallbladder,⁴⁸ pancreas^{48 90-96} and breast,⁴⁸ in peritoneal mesothelioma⁹⁷ and in liposarcoma.⁹⁸ However, TATE and TABE often occur independently and the circumstances in which they arise differ. Most neoplastic cases with a marked blood eosinophilia have late disease with widespread metastases.^{35 48 53 87 99} While some of these cases also show TATE, many do not. Blood eosinophilia has been described as a useful marker of tumour persistence after radiotherapy⁸⁴ and may be absent until recurrence occurs.²⁸ This is of limited application however as radiotherapy especially to the abdomen and pelvis may itself cause blood eosinophilia.¹⁰⁰⁻¹⁰⁴ This radiation-related eosinophilia was found to be associated with a significantly better prognosis in patients with

ovarian and endometrial carcinomas.¹⁰¹

The pathogenesis of blood eosinophilia is not known. Many authors^{48 72 74 76 87 105 106} have linked its presence with necrosis in the primary tumour or in metastases or, in the case of carcinoma of the pancreas, with widespread fat necrosis.⁹⁰⁻⁹⁶ Metastatic carcinoma may also produce an increase in bone marrow eosinophils.¹⁰⁷ Hypoxia,^{108 109} and cigarette smoking¹¹⁰ may cause blood eosinophilia and may possibly contribute to TABE in carcinoma of the lung. Chemotaxis for eosinophils by T lymphocytes¹¹¹ and antigen/antibody complexes¹¹² has been described. It is suggested that immune complex formation with tumour antigen may produce large amounts of C3a, with subsequent histamine release, and perhaps account for the occasional finding of a Loeffler-like endocarditis in patients with marked blood eosinophilia and carcinoma.^{39 113 114}

Conclusion

Tumour-associated eosinophilia is an easily recognisable, but uncommon occurrence. Confusion about its significance in earlier reports in part resulted from failure to distinguish between tissue and blood eosinophilia. Taken separately, TATE without TABE is usually associated with a good prognosis, and TABE with a bad one. Tumour metastases are more commonly seen with TABE, but there is no evidence that the eosinophilia itself contributes to the increase in morbidity, except in the rare cases of eosinophilia-associated endomyocardial fibrosis. The most common site for TATE is in carcinoma of the cervix, in which the histological appearance of the tumours with eosinophilia is distinct and characteristic.

This tissue reaction might represent a specific response to tumours by a small percentage of the population, who would presumably react to any tumour in a similar way. Alternatively, the tissue eosinophilia might be analogous with local lymphocytic infiltration around tumours, as in medullary carcinoma of the breast, seminoma and nasopharyngeal carcinoma. The TATE would then be due either to secretion of an eosinophilotactic substance by the tumour cells or to local trapping of eosinophils by the tumour or tumour stroma. The first seems most likely, especially as such an attractant has been described.⁸⁸

It has not been possible to distinguish by cell morphology between tumours which have TATE and those of similar histological type which do not, though when TATE occurs the histological appearance is striking. The role of the eosinophil in tumours needs more investigation, both morphologically and immunologically, preferably as Cohen⁸ suggests, "where the action is, at the affected tissue site."

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Requests for reprints to: Dr D Lowe, Department of Histopathology, St Thomas's Hospital Medical School, London SE1 7EH, England.