

Selective peripheral blood eosinophilia associated with survival advantage in Hodgkin's disease (BNLI Report No 31)

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SUMMARY A peripheral blood eosinophilia was found at presentation in 193 of 1260 (15%) patients with Hodgkin's disease who had been entered into clinical studies by the British National Lymphoma Investigation (BNLI). Eosinophilia as a component of a general leucocytosis conferred no survival advantage. Eosinophilia without a general leucocytosis was present in 95 patients, and this selective eosinophilia was associated with a clear survival advantage. The association of selective eosinophilia and improved survival was limited to patients with mixed cellularity and grade I nodular sclerosis histology. Selective eosinophilia was found to be a good prognostic indicator both in local and generalised disease. Its survival advantage seemed to lie in the response to second line treatment following relapse.

Peripheral blood eosinophilia is a well recognised feature of Hodgkin's disease, as is an eosinophilia infiltrate of the disease in lymph nodes and tissues.¹ In this study we evaluated the distribution and clinical importance of blood eosinophilia in 1260 patients with Hodgkin's disease who had been entered into British National Lymphoma Investigation (BNLI)² clinical studies. Patients with eosinophilia were subdivided into two groups: those with a selective eosinophilia and those in whom the eosinophilia was an element of generalised leucocytosis.

Material and methods

The absolute eosinophilia count at presentation was derived from the total white cell count and differential and was available for 1260 patients entered into the BNLI Hodgkin's disease studies over the past 14 years. A raised eosinophil count was taken as greater than $0.44 \times 10^9/l$, and a raised total white cell count as greater than $11 \times 10^9/l$. Eosinophilia associated with a raised total white cell count was taken as an element of general leucocytosis, unless the raised

count was due solely to the eosinophilia. Survival curves were calculated by the life table method, and statistical comparison of curves carried out by the log rank test, as described by Peto *et al*³ and by the Mantel test.⁴ The histopathological subtyping of the patients had previously been determined by the method of Bennett *et al*.⁵⁻⁷

Results

One hundred and ninety three (15%) of the 1260 patients with a recorded eosinophil count had an eosinophilia at presentation. Fig 1 shows the distribution of the eosinophil count. In over 50% of the cases of eosinophilia the count was $> 0.6 \times 10^9/l$. The survival of these patients was found to be significantly greater than that of the remainder ($\chi^2 = 5.0$, fig 2). Of the 193 patients with an eosinophilia, this was part of a general leucocytosis in 98 (51%). In the remaining 95 patients the eosinophilia was selective in that it was associated with a normal total white cell count, or with a raised count due solely to the eosinophilia (two patients). Eosinophilia as part of a general leucocytosis was found to confer no survival advantage ($\chi^2 = 0.0$), whereas selective eosinophilia

showed a clear and significant advantage ($\chi^2 = 8.2$, $p < 0.01$, fig 3). Of the 17 deaths in patients with a selective eosinophilia, four were intercurrent (all in patients with advanced stage and grade I nodular sclerotic histology).

This improved prognosis associated with a selective eosinophilia was present in patients with localised dis-

ease, though not at a significant level ($\chi^2 = 3.4$); in patients with generalised disease the difference was larger and was significant ($\chi^2 = 5.7$, fig 4).

The table shows the incidence of eosinophilia in the different histological groups of Hodgkin's disease. Eosinophilia was absent in patients with lymphocyte depleted histology. In the other histological groups

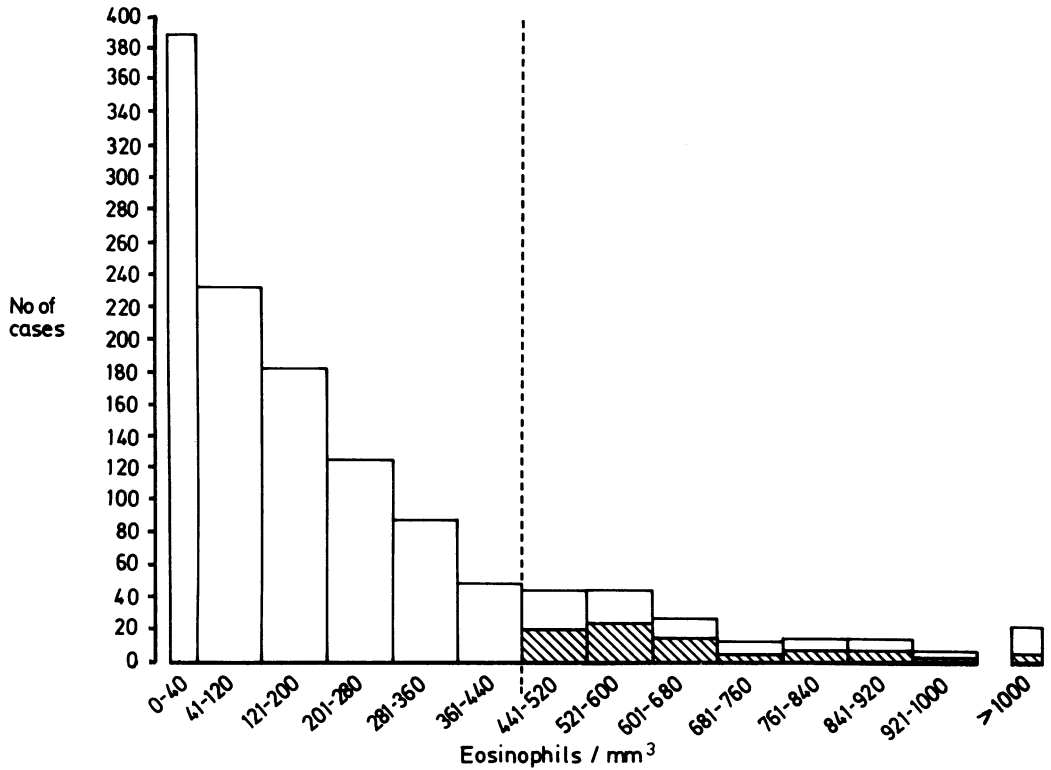


Fig 1 Distribution of eosinophil counts. Shading indicates distribution of selective counts.

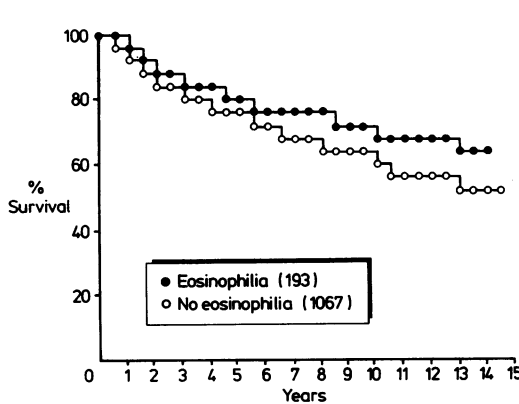


Fig 2 Survival of patients with and without eosinophilia.

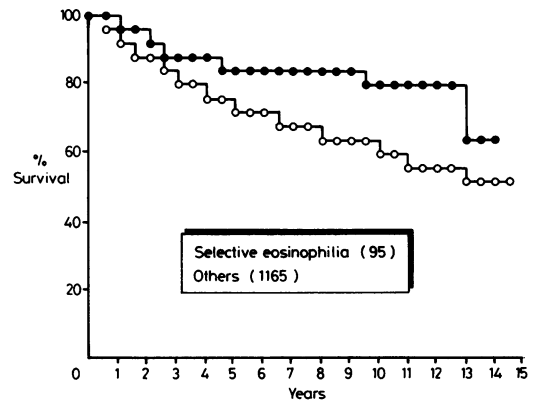


Fig 3 Survival of patients with and without selective eosinophilia.

Table Incidence of eosinophilia in histopathological subtypes

	Total No of patients	Patients with eosinophilia (%)	Patients with selective eosinophilia (%)
Lymphocyte predominant	57	8 (14)	7 (12)
Mixed cellularity	222	22 (10)	18 (8)
Lymphocyte depleted	21	0	0
Grade I nodular sclerosis	671	115 (17)	54 (8)
Grade II nodular sclerosis	270	48 (18)	16 (6)

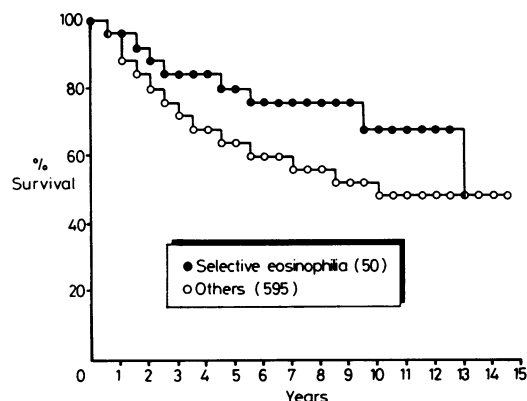


Fig 4 Survival of patients with and without selective eosinophilia in advanced disease.

Discussion

The incidence of eosinophilia at presentation in this very large series of patients with Hodgkin's disease was 15%, which is in agreement with previous estimates.⁸ In patients with an eosinophilia this was selective in almost half (49%) and was part of a general leucocytosis in the remaining 51%. Eosinophilia in general was associated with a minor survival advantage, but the survival advantage for patients with selective eosinophilia was highly significant. The finding that eosinophilia conferred a prognostic advantage is contrary to the findings of Kaplan,¹ who in a major review of Hodgkin's disease concluded that there was no evidence that blood eosinophilia was correlated with prognosis, as did Lowe *et al*⁹ in a review of eosinophilia and tumours in general. This may in part be accounted for by the fact that previous authors have not distinguished between the two categories of eosinophilia, only one of which was found to be associated with survival advantage in the present work. It should be noted that the number of neutrophil leucocytes in the blood has no significance with regard to overall prognosis in Hodgkin's disease (unpublished observations), and why only a selective eosinophilia is associated with improved survival is not clear. The data presented here suggest that the mechanisms of eosinophilia induction in the two situations may be different.

Whether the eosinophilia is merely a bystander reaction to the disease process or represents a specific component of an antitumour response is uncertain. It has been suggested that eosinophils may have inhibitory activity towards tumour targets.¹⁰ In cases of carcinoma of the cervix Pastrnak and Jansa¹¹ reported that a tissue of eosinophil reaction was associated with improved prognosis, and Lowe¹² found significantly fewer mitoses and more single cell necrosis in the eosinophilic areas of these tumours. In Hodgkin's disease eosinophils are also often present in the tumour tissue, and are often prominent in areas of tumour necrosis.^{13 14} It is interesting that although selective eosinophilia is associated with an improved prognosis in advanced disease, it is not associated with improved survival in grade II nodular sclerotic disease. The eosinophil response may help to contain even widespread low and intermediate grade disease but is ineffective in the more aggressive grade II nodular sclerotic form.

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the incidence of eosinophilia (selective and non-selective) was slightly higher in patients with nodular sclerosis, but the incidence of selective eosinophilia was similar in all groups.

With regard to the selective eosinophilias, the survival advantage was found to be confined to patients with mixed cellularity disease ($\chi^2 = 3.8$) and grade I nodular sclerosis ($\chi^2 = 6.1$). No improved survival was apparent in patients with grade II nodular sclerosis, nor in those with lymphocyte predominance, though the number of patients in the latter group was small.

Further analysis of the series was made to determine where the prognostic advantage of selective eosinophilia lay in relation to treatment. No significant difference was found between the complete remission rates and relapse free curves of patients with and without selective eosinophilia, nor between the survivals of patients who failed to obtain complete remission after their initial treatment. There was, however, a considerable and significant difference between the survival of patients with and without selective eosinophilia in those who had relapsed after attaining complete remission from their initial treatment ($\chi^2 = 4.4$).

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