Circulating immunoblasts in polymyalgia rheumatica

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Eghtedari, A. A., Esselinckx, W., and Bacon, P. A. (1976). *Annals of the Rheumatic Diseases*, **35**, 158–162. **Circulating immunoblasts in polymyalgia rheumatica.** The percentage of immunoblasts circulating in the peripheral blood has been examined in a group of 29 patients with polymyalgia rheumatica (PMR). Less than 0.5% of immunoblasts were found in healthy young controls, but 18 of 29 unselected patients with PMR were positive when first tested, a similar proportion to that found in rheumatoid arthritis. Raised immunoblasts were found in only one of 12 elderly controls. The presence of circulating immunoblasts correlated with the activity of polymyalgia both as assessed by the erythrocyte sedimentation rate (ESR) and as assessed by an independent clinical observer. This was true in the group overall and in those patients where serial studies were made. Patients studied from the time of disease presentation showed a concurrent fall in ESR and in immunoblasts on starting steroid therapy. Detection of circulating immunoblasts can be a useful additional test in the assessment of disease activity in PMR, especially in cases with a low ESR.

The presence of circulating immunoblasts supports the concept of an immunological aetiology for PMR. This is strengthened by the finding that raised immunoglobulins were more common in patients with circulating immunoblasts.

The aetiology and pathogenesis of polymyalgia rheumatica (PMR) is unknown, though a number of recent observations have suggested a possible immunological basis for this disease. There is a known association with temporal arteritis (Hamrin, Jonsson, and Hellsten, 1968) and immunoglobulin has been found deposited in media of the involved arteries (Liang and Simkin, 1973). Raised levels of circulating immunoglobulins, especially IgM, are found in some patients (Bacon, Doherty, and Zuckerman, 1975). Infiltration of the internal elastic lamina of the arteries by mononuclear cells has also been reported (Parker, Healey, and Wilske, 1972). Most recently a response of peripheral blood lymphocytes to human vascular antigens has been reported using a lymphocyte transformation test (Hazleman, MacLennan, and Esiri, 1975).

The occurrence of large lymphoid cells, with the appearance of immunoblasts, has been reported in the peripheral blood in several types of immunological disease, including rheumatoid arthritis (RA) and systemic lupus erythematosus (Bacon, Sewell, and Crowther, 1975). The presence of these cells is

indicative of an active immunological reaction (Crowther, Fairley, and Sewell, 1969). This study investigates the incidence of circulating immunoblasts in a group of patients with PMR. This has been compared with a clinical assessment of the disease activity and with laboratory parameters, in particular the erythrocyte sedimentation rate (ESR).

Patients and methods

Twenty-nine patients with PMR were studied, 19 females and 10 males, mean age 68 years. Diagnosis was based on accepted clinical criteria (Dixon, 1969; Hunder, Disney, and Ward, 1969). All patients had a negative test for rheumatoid factor. Five patients were seen before and after starting steroid therapy, while all the others were already on treatment, in some cases for more than 2 years. However, disease activity was not adequately suppressed in all patients. Clinical activity was assessed by an independent observer before the blood results were known. Thirty-nine patients with definite or classical RA attending the clinic were also studied for comparison, as were a fresh control population for this study, consisting of 12 apparently healthy subjects aged over 60 years.

Blood studies included estimation of haemoglobin, ESR (Westergren), and immunoglobulins (radial immunodiffusion technique). All tests were performed in the routine laboratories. Immunoblasts were detected in

lymphocytes separated from defibrinated peripheral blood after incubation with carbonyl iron and separation on a Ficoll-Hypaque gradient as described previously (Egtdari, Davis, and Bacon, 1976). Serial studies were performed in a number of patients so that a total of 69 determinations were made in the 29 patients.

Results

The percentage of immunoblasts at the first clinic attendance for PMR patients, RA patients, and controls is shown in Fig. 1. In the PMR group 17 of 29 patients were positive, which compares closely with 22 of 39 patients with RA. One of the 12 controls was positive at a low level, although previous studies had shown young healthy controls to have <0.5%

circulating immunoblasts. It is known that infection can raise the immunoblast level, although this subject did not have overt infection at the time.

The relationship between immunoblasts and ESR was investigated. Fig. 2 shows the percentage of immunoblasts, using the 69 tests performed in PMR patients compared to the ESR measured at the same time. There was a significant correlation between an ESR >25 and immunoblasts levels above 0.5% ($P < 0.01$, χ^2 test with Yates's correction). Nevertheless, raised levels of immunoblasts were found on eight occasions when the ESR was <25. The relationship between ESR and immunoblast level is reinforced in the case of 5 patients who were followed serially with three or more determinations each (Table I). All these patients had persistently raised ESRs in spite of the current low dose of steroid. On each occasion they also had raised immunoblasts.

Serial studies on 5 new patients who presented with active untreated disease are examined in Fig. 3. In these patients the initially raised ESR levels and the raised immunoblast levels fell at the same time (Fig. 3A). The fall in immunoblasts was related to starting steroid therapy (Fig. 3B), although the rate of fall was variable and the numbers increased transiently in 2 patients.

Raised immunoglobulins in one or more class were found in 6 of 18 patients with positive immunoblasts, as compared to 2 of the 11 patients who had negative immunoblasts at the time of first presentation in the clinic (Table II).

The relationship between clinical activity and the presence of circulating immunoblasts is highly significant ($P < 0.001$, χ^2 test with Yates's correction) (Fig. 4). The numbers refer to the total of 70 tests performed. The disease was judged to be clinically active on 31 occasions. Immunoblasts were positive

FIG. 1 Distribution of circulating immunoblasts in polymyalgia rheumatica (PMR) patients, compared to elderly controls and RA patients

FIG. 2 Relationship of immunoblasts to ESR on 69 occasions in PMR. Raised immunoblasts show a significant correlation with an ESR >25

FIG. 3 (a) Inter-relationship of serial estimations of immunoblasts and ESR in the 5 new patients studied before and after steroid therapy. (b) Fall in number of immunoblasts at time intervals after starting therapy in the same 5 patients

Table I Relationship between immunoblasts and ESR in 5 patients with persistently active disease, who had 3 or more serial determinations

Case no.	ESR (mm/h)	Immunoblasts (%)
1		
a	98	3
b	78	4
c	53	4
2		
a	32	1
b	75	1
c	11	1
d	30	1
3		
a	33	2
b	54	1
c	58	1
4		
a	78	3
b	72	3
c	85	3
d	78	2
5		
a	66	2
b	68	2
c	69	1

on 26 of these. Three of the 5 patients with negative immunoblasts but clinically active disease had a raised ESR. Thus a combination of tests, using both ESR and circulating immunoblasts, would have agreed with the clinical diagnosis of activity on 29 of 31 occasions. The disease was judged to be clinically

FIG. 4 Distribution of immunoblasts in patients judged to be clinically active or inactive. There was a statistically significant correlation between raised levels of immunoblasts and clinical activity

Table II Relationship of immunoglobulin levels to presence of immunoblasts at the time of presentation

Immunoblasts	No. of cases	Serum immunoglobulins			
		Total no. of cases with raised immunoglobulins	IgA > 420 (no. of cases)	IgG > 1700 (no. of cases)	IgM > 190 (no. of cases)
+	18	6	2	2	3
-	11	2	—	—	2

inactive on 39 occasions, on 24 of which the immunoblasts were negative, but on 15 were positive. In two patients an unrelated carcinoma and a recent myocardial infarction accounted for raised immunoblast levels. High immunoblast levels were therefore unexplained on 13 occasions. On ten of these the concurrent ESR was >25 although all these patients were being treated with low-dose steroids and had no clinical symptoms.

Discussion

This study has shown circulating immunoblasts to be present in PMR in a similar frequency to that found in patients with RA attending a clinic. The presence of circulating immunoblasts is known to indicate an active immune reaction and this is compatible with recent evidence for an immunological basis for PMR. The association with raised immunoglobulins in some cases lend further support to this concept. The nature of the responsible antigen is currently speculative. There is a strong evidence for reactivity to vascular tissue (Hazleman and others, 1975). However, an infective aetiology has been suggested by several authors (Bell and Klinefelter, 1967; Mowat and Hazleman, 1974). The possibility of bedsonia from exposure to birds has been raised in one study (Fessel, 1969). Recently an increased incidence of antibody to hepatitis B antigen has been found in PMR (Bacon, Doherty, and Zuckerman, 1975). It is likely that PMR represents an abnormal immunological response to infection in an elderly group of patients. The recent report (Rosenthal and others, 1975) of a possible link with a transplantation antigen (HL-A 8) suggests that this may be superimposed on a genetic susceptibility.

In PMR, as in previous studies of RA, the presence

of circulating immunoblasts correlates with other assessments of disease activity. Our cases showed a good correlation with ESR. This is found in the overall group. It is confirmed by serial studies in both the small group of patients with persistently active disease and in the few patients who were followed serially from the initiation of steroid therapy.

The correlation with clinical assessment of activity was also significant. In most cases this agrees with the ESR. However, in two situations the immunoblasts may have particular relevance. Firstly, in the patients with persistently raised immunoblasts, in spite of clinically inactive disease while on steroids. This suggests that the disease may continue to be active, although the symptoms are suppressed by the steroid therapy. Recrudescence of disease may occur on withdrawal of steroids, even several years after the initial presentation (W. Esselinckx, S. M. Doherty, and A. St. J. Dixon, in preparation) and the course is not always benign (Dixon, 1969; Myles, 1975). Secondly, at the other end of the scale are the small number of patients who have clinical activity in the presence of a low ESR. These form a recognized subgroup (Bruk, 1967) but the clinical diagnosis is difficult to substantiate in the absence of confirmatory laboratory tests. The majority of these patients appear to have raised immunoblasts. This test may, therefore, be of clinical relevance in this subgroup in whom management is often difficult.

We are grateful to the Arthritis and Rheumatism Council and to the South West Regional Hospital Board for generous support. We thank Mrs. Elizabeth Collins for help with statistics and Dr. A. St. J. Dixon for helpful discussion. We are grateful to Dr. A. St. J. Dixon and Dr. J. A. Cosh for allowing us to study patients under their care.

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