Proc EDTA–ERA (1985) Vol 22

T LYMPHOCYTE AND MACROPHAGE INVOLVEMENT IN THE GLOMERULAR LESIONS OF MICROSCOPIC POLYARTERITIS

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Summary

We employed cell-specific monoclonal antibodies to study the presence of T lymphocytes and macrophages in the glomeruli of five patients with microscopic polyarteritis and crescentic nephritis, showing minimal or absent glomerular immune deposits. Biopsies from patients with active disease (4 cases) showed large numbers of intra-glomerular monocyte/macrophages (representing the predominant cell type) and T lymphocytes (with T cytotoxic/suppressor predominance). In contrast only few of these cells were detected in the glomeruli in the patient with inactive disease. This similar occurrence of T cells and macrophages in the earlier periods of active disease, despite the absence of glomerular immune deposits, and their decrease thereafter, supports a role for cellular immune mechanisms in the pathogenesis of the glomerular lesions.

Introduction

Renal lesions are frequently encountered in microscopic polyarteritis [1,2]. Vascular involvement is usually confined to small vessels [1,2] with focal destruction of the internal elastica lamina and/or necrotizing glomerular lesions with crescent formation [1–3]. Typically immune deposits are either minimal or absent and although the pathogenesis of this situation is unknown, an immunological mechanism seems probable. An immune complex mediated mechanism has been suggested [1], but current evidence fails to support it [2,3]. Alternatively cellular immune mechanisms could be predominantly involved [4].

To elucidate these mechanisms, we determined the presence of T lymphocytes and subsets, monocyte/macrophages and other mononuclear leucocytes in the glomeruli of patients with microscopic polyarteritis, and correlated the results with the clinical activity of the disease at the time of biopsy.

Patients and methods

Patients Five adult patients were studied. All presented with renal failure of recent onset, associated with clinical signs of systemic disease (Table I).

TABLE I. Microscopic polyarteritis: clinical and laboratory findings at the time of the biopsies studied with monoclonal antibodies

Number	Name	Age	Sex	Clinical findings	Time from onset	Serum creatinine (μmol/L)
					Active Disease	
1	JT	58	M	ARF+ vasculitic rash + episcleritis	3 weeks	862
2	SH	58	F	Nephritic S + vasculitic rash + nasal discharge	4 weeks	354
3	VK	31	M	ARF + arthritis + fever	12 weeks	459*
4	AM	49	F	Renal failure fever + weight loss + haematuria	18 weeks	250
					Inactive Disease	
5	RS	52	F	Presented with haematuria, vasculitic rash and renal failure (creatinine=284). Spontaneous improvement over the next months	12 months	147

*on haemodialysis

Biopsies Renal biopsies obtained at initial presentation (Table II) showed extensive glomerular crescents, associated with segmental tuft necrosis in two cases. Glomerular immune deposits were sought by conventional immunoperoxidase studies using commercially available antisera, but were absent in the majority and minimal in two patients. A control biopsy was obtained at 12 months follow-up in the fifth patient, at a time of clinical quiescence following spontaneous improvement.

Renal tissue obtained at the time of initial presentation in patients 1 to 4

TABLE II. Microscopic polyarteritis: histological findings at presentation and at the time of the study with monoclonal antibodies

Number	Glomeruli	Immune deposits	Vessels	Interstitium
		Active Disease		
1	Fifty-five per cent with fibrocellular crescents	2/6 – segmental IgM	Normal	Focal scarring, patchy infiltrate
2	31/32 – with segmental tuft necrosis and crescents	Absent	Elastic reduplication	Slight infiltrate
3	One hundred per cent fibrocellular crescents	Absent	Normal	Slight infiltrate + fibrosis
4	Sixty-six per cent fibrocellular crescents. Fibrinoid necrosis	1/4 – segmental IgM	Focal destruction of inter-elastic in interlobular arteries	Severe scarring
		Inactive Disease		
5 (Initial biopsy at 6 weeks)	Sixty per cent fibrocellular crescents. Segmental proliferative lesions	Absent	Normal	Diffuse fibrosis
Control biopsy (at 12 months)	Forty per cent obsolete. Segmental capsular adhesions	Absent	Focal destruction of elastic laminae	Extensive scarring

(active disease), and the control biopsy in patient 5 (inactive disease) were studied with monoclonal antibodies.

Monoclonal antibodies A panel of previously well-characterized monoclonal antibodies (McAb) was applied at appropriate dilutions to sequential cryostat sections, and revealed using an indirect immunoperoxidase technique. Sections were counterstained with Mayer's haemaleum. Both positive and negative controls were used for each monoclonal antibody and for each biopsy. We employed McAb recognizing epitopes expressed in all leucocytes (2DI); monocyte/macrophages (FMC 32); all T lymphocytes (Ucht 1); T helper/inducer (Leu 3a); T cytotoxic/suppressor (Ucht 4); natural killer cells (Leu 7); and B lymphocytes (TO 15). Results were expressed as the number of positive cells per glomerular cross-section. This was determined counting in each section the total number of positive cells with each McAb, and the number of glomeruli present.

Results

Results are shown in Figures 1 and 2. Significant numbers of intra-glomerular leucocytes were seen in all biopsies (mean 45.4±27 leucocytes/glomerular cross section), with monocyte/macrophages representing the predominant cell

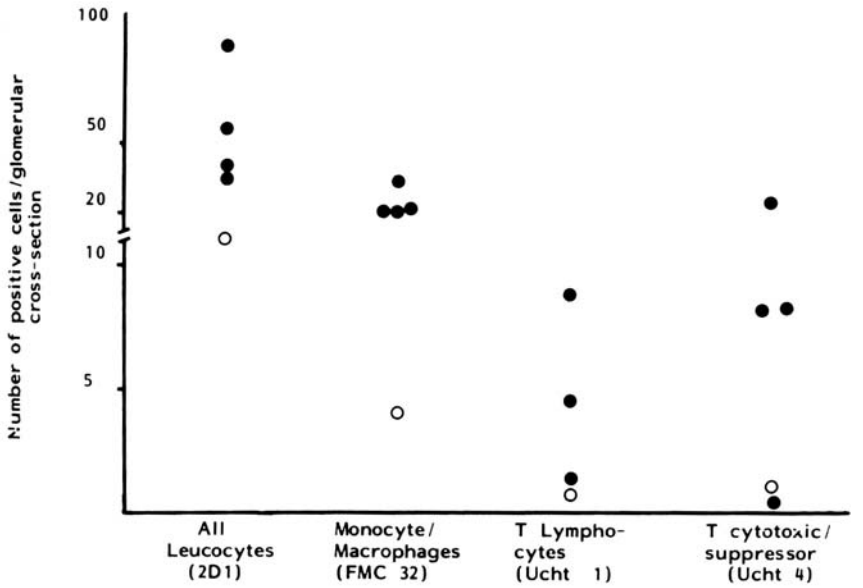

Figure 1. Numbers of intraglomerular leucocytes, monocyte/macrophages, T lymphocytes and T cytotoxic/suppressor cells in active (•) and inactive (○) microscopic polyarteritis

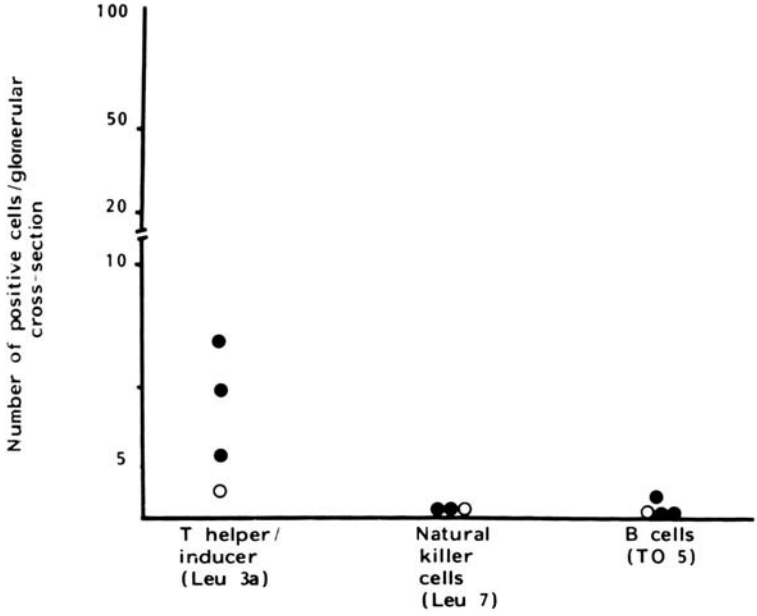

Figure 2. Numbers of intraglomerular T helper/inducer lymphocytes, natural killer cells, and B lymphocytes in active (•) and inactive (○) microscopic polyarteritis

type studied (19±10/glomerular cross section). B cells and natural killer cells were absent from the glomeruli of these biopsies.

However the results in biopsies obtained at a phase of clinical activity (patients 1 to 4), contrasted with the ones encountered in the inactive biopsy (patient 5). Active disease was associated with substantially higher numbers of intra-glomerular leucocytes (54±23), monocyte/macrophages (23±5.6), T lymphocytes (5±3.5), T cytotoxic/suppressor (9.4±9) and T helper/inducer cells (5±2). T cytotoxic/ suppressor cells predominated over T helper/inducer cells in this group, but both cell types were present in similar numbers in the inactive biopsy. Monocyte/ macrophages were the predominant cell type in both active and inactive biopsies.

Discussion

Our results indicate that a significant intra-glomerular influx of circulating mononuclear leucocytes (T cells and monocyte/macrophages) occurs during the initial active stages of microscopic polyarteritis. During this period T cytotoxic/ suppressor cells predominated over T helper/inducer cells.

This cellular influx subsequently decreases, when the development of a quiescent state takes place. Only one biopsy was analysed at a period of inactive disease, but the differences to the active group, both in the numbers of T lymphocytes and macrophages were striking.

The involvement of T cells in human glomerular lesions, although suggested,

awaits confirmation [4]. However, experimental data indicate that these cells are involved in the appearance of the glomerular lesions in a rat model of autologous anti GBM glomerulonephritis [5]. In this study T cells could be demonstrated inside the glomeruli, where they preceded the influx of macrophages. Administration of Cyclosporin A prevented this appearance of intra-glomerular T cells and the subsequent macrophage-induced lesion [5].

Despite the absence of glomerular immune deposits, our findings were similar in several ways. Firstly the number of intra-glomerular T lymphocytes depended on the activity of the disease, decreasing when quiescence was reached. Secondly the changes in the number of T cells were in parallel with those seen in macrophages. Taken together all these findings suggest an association between T cells, monocyte/macrophages and the glomerular lesions seen in our patients [5].

Cells belonging to the monocyte/macrophage lineage were prominent among the various cell types studied. These cells are probably circulating monocytes infiltrating the glomerulus, although we can not exclude an increase in the number of any possible resident glomerular macrophages. Similar results have been obtained by others in patients with various types of crescentic nephritis [6 8], although no reports are available specifically studying biopsies from patients with microscopic polyarteritis.

Experimental studies suggest that macrophages can be involved in the development of glomerular injury [9]. However, the mechanisms responsible for their accumulation in glomeruli are unknown [4]. Among the suggested possibilities [4,6], an Fc or complement dependent adherence, seems unlikely in our patients due to the absence of immune deposits. Alternatively activated T cells could be responsible for the glomerular influx of macrophages [1,4 6]. Our results support this latter hypothesis, suggesting a role for a T cell dependent mechanism in the pathogenesis of these glomerular lesions.

The increased numbers of T helper/inducer cells could perhaps indicate a persistent stimulation of cellular immune mechanism, attracting macrophages to the glomeruli [5]. This latter cell type, together with the T cytotoxic/suppressor cells could in turn be responsible for the appearance of the necrotizing lesions, characteristic of this situation [1].

Thus cellular immune mechanisms could represent the predominant or sole pathogenic mechanism in glomerular lesions of microscopic polyarteritis [1], and perhaps in other vasculitic diseases [1,4]. In fact T cells and macrophages have been demonstrated to be the predominating cell types infiltrating pulmonary arteries in a case of Wegener's granulomatosis, in the absence of local immune complex deposition [10].

Acknowledgments

Dr F Nolasco was supported during part of this work by a British Council Scholarship.

Monoclonal antibodies 2DI, Ucht 1, Ucht 4, TO 15 and FMC 32 were kind gifts of Drs P Beverley, D Mason and H Zola respectively.

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