CLINICAL INVESTIGATION

Characterization of mononuclear cell subsets in renal cellular interstitial infiltrates

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Characterization of mononuclear cell subsets in renal interstitial infiltrates. Indirect immunoperoxydase analysis using monoclonal antibodies (Mo Ab) was performed in 33 renal biopsies with interstitial cellular infiltration obtained from non-transplanted patients. We reviewed four acute interstitial nephritis (IN), three chronic IN, four granulomatous IN, four acute tubular necrosis, four vasculitis, seven primary glomerulonephritis and seven active lupus nephritis (LN). We used Mo Ab recognizing T and B cell markers [OKT3, OKT8, T4, B_1, IOT_{14} (IL_2 receptor)], HLA-DR related antigen (I_2) and monocytes/macrophages (LeuM$_3$). In all cases the interstitial cellular infiltrates were predominantly T cells, whereas the B cell population accounted for less than 20% of the infiltrate. LeuM$_3^+$ cells were present in 28 of 32 cases, usually in a lesser proportion than T cells. IOT_{14}^+ cells were exceptional. $T4^+/T8^+$ cells were clearly greater than one in three acute IN, three granulomatous IN, two LN and two vasculitis. The $T8^+$ cell population predominated in one case of chronic IN related to a non-steroidal anti-inflammatory drug. In all the remaining cases T4+ and T8+ cells were equally present. Aberrant strong HLA-DR expression within tubular cells was noted in nine cases (4 LN) irrespective of the presence of tubular lesions. On the basis of the phenotypic analysis, our data do not support a specific pattern of the infiltrate in regard to a given etiology and thus cannot be used as a diagnostic tool. However, such analysis may aid in understanding the mechanisms of tissue injury.

In addition to the special case of allograft rejection, the renal interstitium may be the site of cellular infiltration and consistent injury in various pathological conditions, including primary tubulo-interstitial diseases, glomerulonephritis, and systemic diseases [1]. In some circumstances immunofluorescence study reveals granular or linear IgG fixation along the renal tubules suggestive of an underlying immune humoral mechanism. However, in the majority of cases immunofluorescence is negative, and the role of cell–mediated immunity is then evoked [2]. Using morphological criteria, the characterization of the mononuclear population invading the interstitium is limited. The recent availability of monoclonal antibodies recognizing cell surface antigens gives the opportunity of characterizing the renal cell infiltrates and may aid in understanding the mechanisms of tissue injury.

Methods

Thirty–three renal biopsies were selected on the basis of: presence of significant interstitial infiltrate and availability of

Table 1. Characteristics of the monoclonal antibodies.

Monoclonal AB	AG Molecular wt *daltons*	Ig Class *mouse*	Specificity	Source
OKT3	19,000	Ig G_{2a}	Pan T cells	Ortho immune
T4	64,000	IgG_1	T helper/inducer cells	Coulter electronics
OKT8	70,000	IgG_{2a}	T suppressor/ cytotoxic cells	Ortho immune
LeuM$_3$	—	IgG_{2b}	Monocytes/ macrophages	Becton Dickinson
I_2	29,000 32,000	IgG_{2a}	HLA-DR related Ia–like antigen	Coulter electronics
IOB_1	—	IgG_{2a}	Pan B cells	Immunotech
IOT_{14}	55,000	IgG_{2a}	Interleukin 2 receptor	Immunotech

Abbreviations are: AB, antibody; AG, antigen; Ig, immunoglobulin.

sufficient material. Using these criteria, we reviewed four acute interstitial nephritis (AIN), three chronic interstitial nephritis (CIN), four granulomatous interstitial nephritis (GIN) (characterized by the presence of epitheloid and giant cell granulomas), four acute tubular necrosis (ATN), four vasculitis, seven primary glomerulonephritis and seven active lupus nephritis (LN). Unaffected portions of two adult kidneys obtained by nephrectomy for cancer were used as normal controls.

Morphological methods

All renal specimens were processed for light microscopy and immunofluorescence. Cryostat sections were examined by using commercial monospecific antisera directed against human IgG, IgM, IgA, Clq, C3, C4, Fibrin and albumin (Behringwerke, Marburg, FRG, and Hyland Laboratories, Costa Mesa, California, USA). All biopsies were evaluated with regard to primary lesions and the extension and density of the interstitial cellular infiltration and the presence of tubular lesions or tubular atrophy. The following scale was employed: 0 = none; 1 = focal; 2 = diffuse but moderate; 3 = diffuse and severe.

Immunoperoxydase technique

Phenotypic characterization of the infiltrate was accomplished by using a three–step immunoperoxydase technique previously described [3]. Briefly, 2 μ thick cryostat sections

Table 2. Phenotypic analysis of the renal interstitial infiltrates.

	Pts	Age/Sex	Etiology	Cell infil.	Tubular		OKT3	T4	OKT8	LeuM₃	IOB₁	IOT₁₄	I₂
					N	A							
AIN	1	42/F	Septicemia	3	2	1	+ + + + (52 ± 5)	+ + + + (49 ± 2)	+ + + (26 ± 7)	+ + + (25 ± 6)	+ + (15 ± 5)	ND	+ + + (42 ± 13)
	2	37/M	Penicillin V	2	2	0	+ + + (40 ± 3)	+ + + (34 ± 1)	+ + (17 ± 8)	−	−	−	+ + (20 ± 10)
	3	66/M	Septicemia	2	2	0	+ + (17 ± 3)	+ + (18 ± 6)	+ + (15 ± 7)	+ + (14 ± 6)	+ + (15 ± 5)	+ (5 ± 1)	+ + (21 ± 11)
	4	33/F	Uveitis	3	3	0	+ + + + (56 ± 7)	+ + + + (51 ± 3)	+ + + (25 ± 4)	+ + + (26 ± 6)	+ + (14 ± 4)	−	+ + + (37 ± 8)
GIN	5	30/M	Sarcoidosis	2	2	3	+ + (22 ± 8)	+ + + (36 ± 5)	+ + (17 ± 2)	+ + (21 ± 7)	−	−	+ + + (42 ± 4)
	6	30/M	Uveitis	2	3	3	+ + (18 ± 4)	+ + (22 ± 12)	+ + (20 ± 4)	−	−	−	+ + (21 ± 10)
	7	55/F	Sarcoidosis	2	2	0	+ + (22 ± 3)	+ + + (42 ± 2)	+ + (20 ± 2)	+ (8 ± 2)	+ (5 ± 2)	−	+ + + (39 ± 11)
	8	57/F	Sarcoidosis	2	2	2	+ + (18 ± 9)	+ + + (38 ± 5)	+ (11 ± 4)	+ + (19 ± 3)	+ (3 ± 1)	−	+ + + (37 ± 7)
ATN	9	31/M	Indomethacin	1	2	0	+ + (21 ± 1)	+ + (19 ± 7)	+ + (16 ± 5)	−	+ + (17 ± 3)	−	+ (8 ± 6)
	10	53/F	Glafenin	1	2	0	−	−	+ + + + (60 ± 3)	−	−	−	−
	11	19/F	Glafenin	1	2	0	+ (8 ± 2)	+ (11 ± 4)	+ (9 ± 1)	+ + + (25 ± 3)	−	ND	+ + + (30 ± 10)
	12	20/M	Glafenin	1	2	0	+ + (20 ± 4)	+ + (21 ± 6)	+ + (18 ± 5)	+ (8 ± 1)	−	−	+ + (15 ± 7)
CIN	13	44/F	Phenacetin Aspirin	2	0	3	+ + (20 ± 11)	+ + (21 ± 10)	+ + (17 ± 2)	+ + (17 ± 6)	+ (7 ± 11)	ND	+ + (21 ± 5)
	14	42/M	Aspirin	2	0	3	+ (7 ± 2)	+ + (21 ± 5)	+ + (19 ± 2)	+ (6 ± 1)	−	−	+ + (19 ± 4)
	15	20/M	Indomethacin	2	2	3	+ + (22 ± 5)	+ (9 ± 5)	+ + + (29 ± 4)	+ + (17 ± 3)	+ + (16 ± 2)	−	+ + + (27 ± 6)

Abbreviations are: Pts, patients; cell infil., interstitial cell infiltrate; N, necrosis; A, atrophy; ECG, extracapillary proliferative glomerul onephritis; ATIN, acute tubulo-interstitial nephritis; focal GN, focal proliferative GN; diffuse GN, diffuse proliferative GN; FSG, focal glomerular sclerosis; AGN, acute post-infectious GN; MPGN, membranoproliferative GN; ND, not done.

were air–dried, fixed by acetone and stored at −80°C until use. Before staining, the slides were re-fixed in chloroform, air-dried and washed in tris-NaCl buffer at pH 7.40. The appropriate dilution of each monoclonal antibody was applied and incubated during 30 min in a moist chamber. The sections were washed again in tris-NaCl buffer and incubated with anti-mouse IgG peroxydase conjugated rabbit IgG (Dako Laboratories, Copenhagen, Denmark) for 30 min. After washing in tris-NaCl, slides were incubated with anti-rabbit IgG peroxydase conjugated goat IgG (Nordic Laboratories) for 30 min and washed again in tris-NaCl. The final reaction was achieved by incubating the sections with 3 amino 9 ethyl carbazol and 0.01% hydrogen peroxyde for 15 min. Then the sections were washed in tris-NaCl buffer and finally counter–stained with Mayer's hemalun for 10 min. For each biopsy specimen, the control slide was submitted to the same technique except for the omission of the monoclonal antibody.

Characterization of inflammatory cell subsets

We used a panel of commercial monoclonal antibodies (Mo Ab) of known specificity: OKT3, OKT8, T4, LeuM₃, IOB₁, IOT₁₄ and I₂. The characteristics of these monoclonal antibodies are summarized in Table 1. Appropriate dilution of each monoclonal antibody was determined by titration performed on normal human lymphoid tissue and blood smears. All tissue sections were examined by two observers. Cells were scored positive only if they displayed distinct membrane staining. Semi-quantitative analysis was performed by enumerating positive cells per 100% in five fields at 400 high power. Serial sections allowed estimation of the same fields with different monoclonal antibodies. When discordant results were obtained between the two observers, all the positive cells of the whole slide were enumerated. The initial percentage values were then transformed into a plus system in order to facilitate reading of results: + for occasional cells; + + for less than 20% of interstitial cells stained; + + + for 20 to 50%; and + + + + for more than 50%.

Patients. Details concerning sex, age, etiology and histological diagnosis are summarized in Tables 2 and 3.

Results

Normal kidneys

No staining of native renal structure was observed with OKT3, T4, OKT8, LeuM₃, IOB₁ and IOT₁₄ Mo Ab. Anti HLA-DR Mo Ab revealed intense staining of endothelial cells along the glomerular capillary loops and the peritubular capillaries, whereas a faint staining was present on the endothelium

Table 3. Phenotypic analysis of the renal interstitial infiltrates.

	Pts	Age/sex	Lesions	Cell infil.	Tubular N	Tubular A	OKT3	T4	OKT8	LeuM$_3$	IOB$_1$	IOT$_{14}$	I$_2$
Vasculitis	16	45 M	ECG	3	3	2	−	+ + + (34 ± 5)	+ + (18 ± 3)	+ + + (33 ± 10)	+ + (17 ± 2)	+ (3 ± 1)	+ + (22 ± 11)
	17	81/M	ECG	3	2	3	+ + + (35 ± 4)	+ + + (38 ± 4)	+ + (20 ± 5)	+ (7 ± 2)	−	−	+ + + (36 ± 12)
	18	55/M	ECG	3	3	0	+ + (19 ± 8)	+ + (21 ± 7)	+ + (15 ± 2)	+ + (17 ± 6)	+ (10 ± 5)	+ (2 ± 1)	+ (8 ± 4)
	19	70/F	ECG	2	2	2	+ + (20 ± 9)	+ + (19 ± 11)	+ + (16 ± 6)	+ + + (32 ± 8)	+ (8 ± 3)	+ (4 ± 1)	+ + + (41 ± 7)
LN	20	42/M	ATIN	3	2	0	+ + (18 ± 5)	+ + (20 ± 7)	+ + (20 ± 2)	+ + + (26 ± 5)	+ + (15 ± 1)	+ (2 ± 1)	+ + + (42 ± 6)
	21	46/F	ATIN	3	2	2	+ + (17 ± 5)	+ + + (29 ± 5)	+ + (15 ± 6)	+ + + (25 ± 6)	+ (7 ± 2)	−	+ + + (30 ± 8)
	22	24/F	focal GN	2	0	3	+ + (18 ± 4)	+ + + (33 ± 6)	+ + (16 ± 3)	+ + (20 ± 6)	+ (9 ± 3)	ND	+ + (15 ± 5)
	23	21/M	focal GN	2	0	0	+ + (21 ± 5)	+ + (21 ± 8)	+ + (18 ± 7)	+ + (17 ± 8)	−	−	+ + (22 ± 4)
	24	24/F	diffuse GN	3	2	0	+ + + (33 ± 2)	+ + + (32 ± 4)	+ + + (28 ± 3)	+ + + (25 ± 4)	+ + (15 ± 5)	−	+ + + (38 ± 9)
	25	52/M	diffuse GN	3	0	3	+ + (17 ± 4)	+ + + (26 ± 3)	+ + + (28 ± 5)	+ + + (28 ± 7)	+ (4 ± 1)	+ (6 ± 2)	+ + (22 ± 13)
	26	52/M	diffuse GN	3	0	3	+ + (20 ± 5)	+ + (21 ± 6)	+ + (22 ± 4)	+ + + (32 ± 6)	−	ND	+ + (15 ± 3)
Glomerulo-nephritis	27	70/F	FSG	2	0	2	+ + (19 ± 3)	+ + (18 ± 9)	+ + (22 ± 5)	+ (9 ± 2)	−	−	+ (11 ± 6)
	28	37/M	AGN	2	2	0	+ (6 ± 3)	+ (10 ± 2)	+ (7 ± 1)	+ (10 ± 4)	−	−	+ (11 ± 6)
	29	22/F	AGN	3	1	0	+ + (17 ± 1)	+ + + (25 ± 7)	+ + (19 ± 1)	+ + (21 ± 1)	−	−	+ + (18 ± 6)
	30	43/M	MPGN	2	0	3	+ + (20 ± 5)	+ + (15 ± 6)	+ (9 ± 2)	+ + (17 ± 2)	+ (3 ± 1)	−	+ + (19 ± 7)
	31	50/M	MPGN	2	0	2	+ + (15 ± 4)	+ + (16 ± 2)	+ + (15 ± 3)	+ + (18 ± 5)	−	−	+ + (20 ± 5)
	32	49/M	cryoglobu-linemia	2	0	2	+ (9 ± 2)	+ + (23 ± 5)	+ + (17 ± 2)	+ + (17 ± 7)	−	ND	+ + (20 ± 7)
	33	63/M	MPGN	2	0	0	+ + (15 ± 1)	+ + (14 ± 3)	+ + (8 ± 1)	ND	ND	ND	+ + (21 ± 5)

For abbreviations, refer to Table 2.

of interlobular arteries. Staining of mesangial areas, presumably mesangial cells or expansion of endothelial cytoplasma, was always observed (Fig. 1). Lacis areas were negative. Some DR-positive stellate forms were present in the interstitium; however, the precise nature of these forms—minute capillaries, monocytes or dentritic cells—could not be definitely assessed by light microscopy. In one case some faint staining was observed with anti-DR Mo Ab within some proximal tubules, mainly at the cellular basal pole. Very few LeuM$_3$ positive cells were observed in the interstitium in the two cases, and were present in some glomeruli in one.

Renal diseases

In all cases (Tables 2 and 3), the infiltrating cells were recognized by light microscopy as mononuclear cells, even in the two cases of septicemia (cases 1 and 3). The extension and density of the infiltrates varied from case to case, being higher in acute interstitial nephritis, vasculitis, lupus nephritis, and in one case of post-streptococcal acute glomerulonephritis. Tubular cell damage was observed in several cases.

By immunofluorescence, no linear IgG fixation was observed along the tubular basement membranes (TBM). In contrast, granular deposits of IgG, C3 and C1q were present along the TBM and in the interstitium in the seven LN cases (20 through 26). Scanty deposits of C3 along the TBM were observed in cases 3, 8, 15, 17, 29 and 30.

Expression of DR Ag on the endothelial cells was similar to that observed in the normal kidney in all but two cases (cases 16 and 18) where it was lacking. DR Ag was strongly expressed within tubular cells mainly proximal tubules, with staining intensification at the periphery of the cells in nine cases (cases 1, 4, 17, 21, 23–25, 29 and 33) (Fig. 2). The presence of DR Ag was not related to the presence or degree of tubular lesions seen in light microscopy.

Characterization of cell infiltrates

In all cases the majority of infiltrating cells were T cells. However, in all cases the number of OKT3 + cells was less than the sum of OKT8$^+$ plus T4$^+$ cells. In cases 10 and 16, OKT3
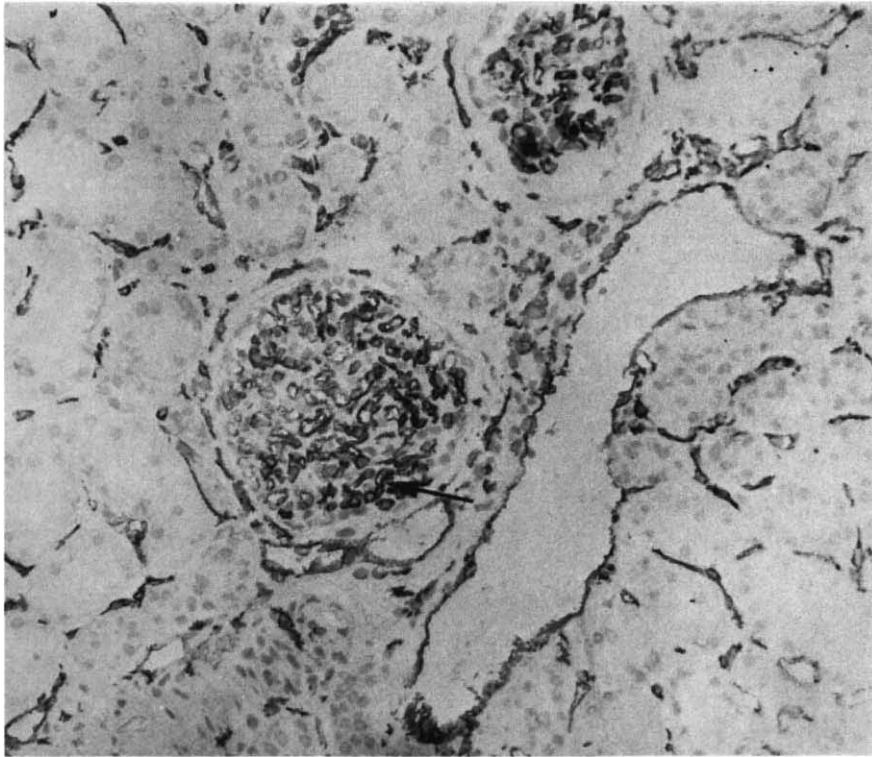
Fig. 1. *HLA-DR antigen expression in adult normal kidney (× 250).* Note the presence of DR antigen on the peritubular veinular and glomerular capillaries. Note also some staining in mesangial areas (↗).
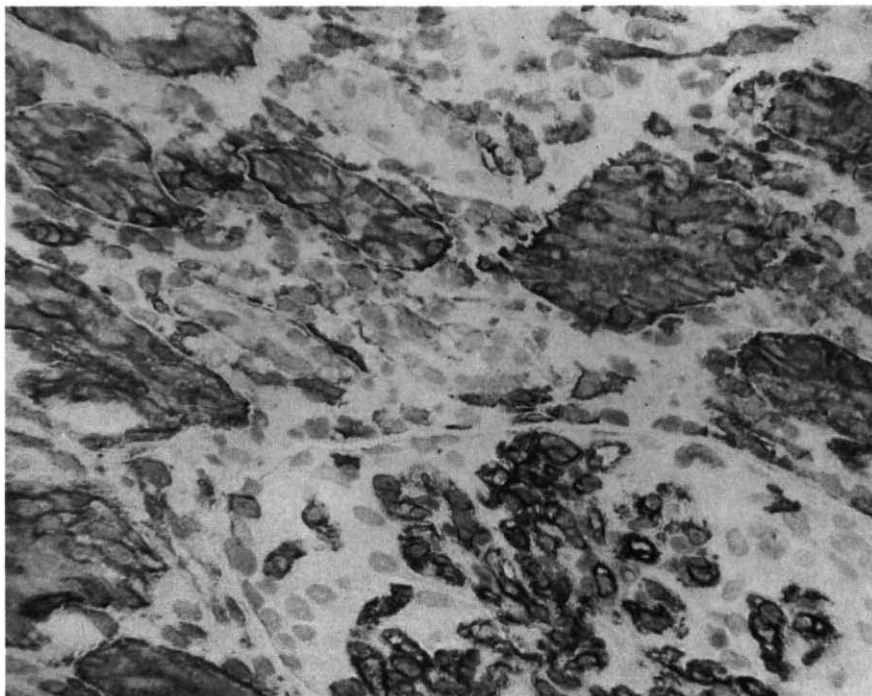

Fig. 2. *HLA-DR antigen expression in case 29 (× 400).* Note the aberrant DR expression by tubular cells.

staining was totally negative. In cases 1, 4 and 15 we observed T cells, either T3$^+$, T4$^+$ or T8$^+$, between the epithelial tubular cells ("tubulitis" lesions). The B$_1$$^+$ cell population always represented less than 20% of the cell infiltrate even in lupus nephritis. Monocytes/macrophages were observed in 28 of 32 cases, usually to a lesser degree than T cells. LeuM$_3$$^+$ cells

were not observed in one case of GIN (case 6) where only disseminated mononuclear cell infiltrate was present in frozen tissue sections. Conversely, in case 5, where two granulomas were examined, the epithelioid cells were LeuM$_3$ and DR-positive. Evaluation of the T cell subsets showed that T4$^+$ cells were present in the same proportion as T8$^+$ cells in the
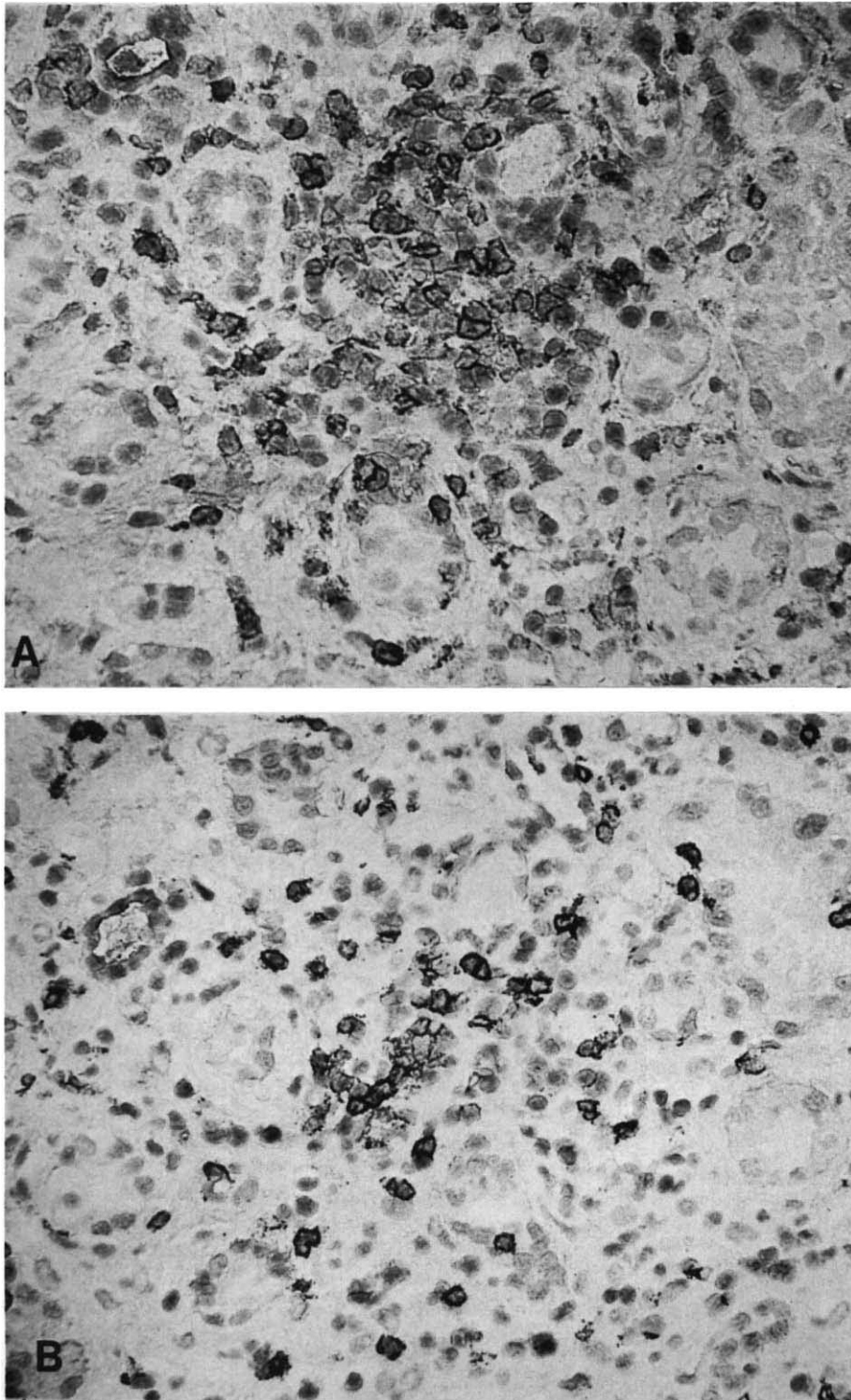
Fig. 3. *Serial sections of renal biopsy obtained from case 4.* **A.** T4+ cells in the renal interstitium (× 400). **B.** T8+ cells in the renal interstitium (× 400).

majority of cases. However, there were a few exceptions: in three of four cases of AIN (1 septicemia, 1 hypersensitivity to penicillin, 1 idiopathic form with uveitis) T4+ cells were clearly more numerous than T8+ cells (Fig. 3). T4+ cells were also clearly more numerous than T8+ cells in three of four GIN and in two of four vasculitis. In LN a slight predominance of the

T4+ population was noted in two cases. Conversely, the T8+ population was prominent in one case of CIN related to a non-steroidal anti-inflammatory drug (case 15) and in one case of ATN with focal interstitial cells related to glafenin (case 10).

Occasional IOT_{14}^+ cells were present in the interstitium in six of 26 cases. However, the sum of B_1^+ plus $LeuM_3^+$ cells

was clearly lower than the number of DR^+ cells in the interstitium in cases 2, 5, 6, 7, 14 and 17.

Discussion

This study was designed to analyze and compare the composition of interstitial inflammatory cell infiltrates occurring in various clinico-pathological conditions. We reviewed 33 renal samples. A panel of Mo Ab was employed to characterize and enumerate immune cell subsets present in tissue sections by dissection of the cell surface antigens. Although the number of cases in each subgroup of diseases was limited, the results described here reveal that whatever the underlying renal disease, the cellular infiltrates were mainly constituted of T cells and monocytic cells. The number of $OKT3^+$ cells was always smaller than the sum of $T4^+$ and $T8^+$ cells. The fact that OKT3 Mo Ab gives a faint staining as compared to T4 and OKT8 Mo Ab may account for this result. However, the presence of $T4^+$ $T8^+$ cells and/or natural killer cells with $T3^-$ $T8^+$ phenotype cannot be excluded [4]. The B cell population always represents less than 20% of the cells. Within the limits of the Mo Ab panel we used, less than 50% of the interstitial cells were identified in cases 6, 11, 12, 14, 28 and 30. Beyond problems of precise delineation of the infiltrates, the presence of non-inflammatory cells such as fibroblasts or proliferative endothelial cells could be relevant to the unstained cell population. Within the T cell population, both T helper/inducer and T cytotoxic/suppressor cells are equally represented in the majority of cases. However, AIN of various etiologies and GIN are characterized by a more marked $T4^+$ subset. Furthermore, we noted that in some active LN, and in half the cases of vasculitis, the $T4^+$ cell population may also be greater in the interstitium as compared to the $T8^+$ population. Conversely, $T8^+$ cells predominate only in one case of CIN related to indomethacin administration.

In some cases the sum of B_1 and $LeuM_3$ cells was less than the DR+ interstitial cell population, which can indicate the presence of activated T cells. However, the presence of activated T cells was rarely demonstrated on the basis of expression of IL_2 receptor. This fact does not negate the presence of activated T cells since the expression of the IL_2 receptor by T cells appears to be a transient phenomenon [5].

DR antigen was strongly expressed by proximal tubular cells in nine cases irrespective of the presence of tubular lesions. It is of note that in six of these nine cases, granular IgG and/or C3 deposits were present along the tubular basement membranes, and that four cases concerned lupus nephritis. It has been suggested that tubular cells may synthesize DR antigen in response to immunological stimulus [6]. Similarly, aberrant DR expression by thyroid epithelial cells has been reported in autoimmune thyroiditis, mainly in Hashimoto's disease [7].

The recent literature contains several studies attempting to characterize a specific pattern of in situ infiltrating cells in renal diseases [2, 8–17] (Table 4). Most of these reports concern AIN and GIN, and in most, the number of cases with precise etiology is small [2, 8–13]. The T cell population is described by all the authors as the prominent cell population invading the interstitium [2, 8–17]. These studies point out the role of cellular mechanisms in inducing and/or perpetuating the renal damage in various conditions, whether or not initiated by humoral mechanisms. Phenotypic characterization of the inflammatory cells involved in the two major types of cell–mediated response

Table 4. In situ T cell subsets in renal diseases, review of the literature.

Ref.	Lesions	Patients, N	Etiology	Results
7	IN	3	Various	T cells Tα cells $Ia^+ T$ cells
8	AIN	2	Fenoprofen	T cells
2	AIN	3	Oxacillin Methicillin Penicillin	T cells $T4^+ > T8^+$
9	AIN	1	Cimetidine	T cells $T8^+ > T4^+$
10		2	Fenoprofen	T cells $T8^+ > T4^+$
11	AIN	1	Idiopathic	T cells $T4^+ > T8^+$
12	AIN	9	6 NSAID 3 idiopathic	{ T cells $T4^+$ $T8^+$ { T cytotoxic
13	AIN	5	3 drug related	T cells $T8^+ > T4^+$
	GN	32		{ T cells $T4^+ > T8^+$ { and $T4^+ = T8^+$
14	GN IN	12		T cells various $T4/T8^+$
15	GN	98	Various	T cells $T4^+ T8^+$
16	LN	13		T cells $T8^+ > T4^+$

Abbreviation IN is interstitial nephritis.

has recently been done using monoclonal antibodies. In the delayed–type hypersensitivity reaction (DTH), in situ enrichment of $T4^+$ cells has been observed [18]. Conversely, cytotoxic reaction as observed in graft vs. host reaction, or in allograft rejection, is associated with in situ $T8^+$ cell predominance [19–21]. In AIN related to penicillin group antibiotic hypersensitivity, we and others found a predominance of $T4^+$ cells (case 2) [2]. This would suggest a DTH-type mediated reaction. The frequent observation of epithelioid and giant cell granuloma, the morphological expression of a DTH reaction in antibiotic AIN hypersensitivity [1], supports this hypothesis. In GIN associated with sarcoidosis we also found numerous $T4^+$ cells in the renal interstitium. A similar phenotypic pattern with large amounts of $T4^+$ cells had already been described in bronchoalveolar lavage and in biopsies from Kveim reaction papules in patients with active sarcoidosis [22, 23]. The $T8^+$ cell predominant population has been found in cimetidine associated AIN [10]. It has therefore been suggested that cimetidine, by acting on the H2 receptor of the lymphocytes, could carry along an immune dysregulation with an imbalance between T helper and T suppressor populations [10]. In interstitial nephritis associated with nonsteroidal anti-inflammatory drugs (NSAID), the renal infiltrates were mainly constituted of $T8^+$ cells [11] which were characterized as cytotoxic cells [13]. This would indicate that T cell subset imbalance could also be related to prostaglandin inhibition [24]. However, Bender et al could not differentiate, on the basis of phenotypic analysis, between NSAID and idiopathic interstitial infiltrates [13]. Moreover, only one of our three cases of CIN related to NSAID showed $T8^+$ cell predominance.

In almost all other pathological conditions where lymphocytes were present in the renal interstitium, $T4^+$ and $T8^+$ cell populations were equally represented [14–16] except for lupus nephritis, where $T8^+$ cells were found predominant [17]. At this

point it appears that the phenotypic characterization of cells invading the renal interstitium cannot be helpful in the etiological diagnosis of the lesions. In fact, renal biopsy gives only a single static image of an evolving process. Sequential study of the development of experimental renal tubulo-interstitial disease has shown the large variability in the inflammatory cell populations according to the time of infiltrate analysis [25]. Furthermore, the phenotypic characteristics of the inflammatory cells do not always correlate with their functional status or effects. Lymphocytes bearing a T4 phenotype may represent a helper cell as well as an inducer of suppressor cells, each leading to opposite effects on the immune response [26]. The functional status of T lymphocytes could be more precisely established by using multiple markers of the cell surface. This could allow better understanding of the diverse immune mechanisms involved in renal tubulo-interstitial lesions and may lead to more specific and effective therapy.

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