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Short communication

Possible role for cytotoxic lymphocytes in the pathogenesis of acute interstitial nephritis after recombinant interleukin-2 treatment for renal cell cancer

L. Th. Vlasveld[1,2], E. van de Wiel-van Kemenade[2], A. J. de Boer[2], J. J. Sein[2], M. P. W. Gallee[3], R. T. Krediet[4], C. J. M. Mellief[2]*, E. M. Rankin[1,2], A. Hekman[2], C. G. Figdor[2]

[1] Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[2] Division of Immunology, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[3] Department of Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[4] Department of Internal Medicine, Academic Medical Centre, Amsterdam, The Netherlands

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Abstract. A patient with renal cell cancer developed acute renal failure due to biopsy-proven acute tubulo-interstitial nephritis (AIN) in the 6th week of continuous infusion of 9×10^6 IU m^{-2} day^{-1} recombinant interleukin-2 (rIL-2). We investigated whether the AIN was the result of a cellular cytotoxic reaction induced by the rIL-2 treatment. The cytolytic activity of cryopreserved peripheral blood lymphocytes (PBL), isolated before and at the end of the rIL-2 treatment (at the time of AIN), was studied after 5 days of culture with or without rIL-2 or anti-CD28 and immobilized anti-CD3 antibodies. The PBL isolated before and at the end of the rIL-2 treatment showed cytolytic activity towards a number of allogeneic targets. However, only the PBL isolated at the end of the rIL-2 treatment showed, when stimulated with rIL-2 in vitro, significant cytolytic activity against an autologous renal cell line cultured from the AIN biopsy specimen and against an allogeneic renal cell cancer cell line. These PBL displayed no enhanced killing capacity towards autologous PBL and the melanoma cell line M14. These observations suggest that the AIN may be the result of a cytotoxic lymphocyte-mediated reaction induced by the rIL-2 treatment.

Key words: Acute interstitial nephritis – Renal cell cancer – Interleukin-2 – Immunotherapy

Introduction

The immunological nature of acute (tubulo)interstitial nephritis (AIN) is well established [20]. Experimental data indicate that the loss of immunological tolerance towards endogenous tubulo-interstitial antigens is the hallmark of the pathogenesis of AIN. Helper ($CD4^+$) T cells, responding to these antigens, may activate B and effector ($CD8^+$) T lymphocytes. Antigen-specific delayed hypersensitivity, cell-mediated cytotoxicity, complement-mediated cytotoxicity or antibody-dependent cellular cytotoxicity (ADCC) may lead to tubulo-interstitial damage. The tubulo-interstitial inflammatory infiltrate mainly consists of macrophages and helper and cytotoxic ($CD8^+$) T lymphocytes and may be associated with the deposition of immune complexes or specific antibodies along the tubular basement membrane, depending on the underlying pathogenic mechanism. In man, antigen-specific cell-mediated injury is most common. The disorder is mostly triggered by an infection or the use of drugs [7, 20].

Immune-mediated renal injury is well documented in patients with cancer including renal cell carcinoma and in patients treated with various modes of immunotherapy [11, 18]. Mostly the renal involvement consists of glomerular damage due to immune-complex deposition. The nature of the antigen is not well established [3, 14]. Tubulo-interstitial abnormalities are uncommon [3], and only a few cases of clinically apparent interstitial nephritis in these patients have been reported [1, 10, 28].

Renal failure occurring during treatment with recombinant interleukin-2 (rIL-2) is mostly attributed to hypoperfusion of the kidneys, and is usually reversible after discontinuation of rIL-2 administration [4, 26]. However, the presence of intrinsic renal lesions is suggested by recent functional studies [25], the occasional occurrence of urine sediment abnormalities [4], proteinuria [2] and biochemical evidence of proximal tubular injury [26]. The pathological features, consisting of interstitial lymphoid infiltrates with tubular dilatation and atrophy, are poorly correlated with the clinically apparent renal dysfunction [16]. Recently, a case of histologically documented AIN has been described in a melanoma patient following treatment with rIL-2 and lymphokine-activated killer cells [10]. We observed a case of acute renal failure due to biopsy-proven acute tubulo-interstitial nephritis (AIN) during treatment with rIL-2 alone for advanced renal cell cancer [8]. In the present study we show that the cytotoxic capacity of in

* *Present address:* Department of Immuno-haematology and Blood Bank, Academic Hospital, Rijnsburgerweg 10, 2333 AA Leiden, the Netherlands

Correspondence to: L. Th. Vlasveld, Department of Medical Oncology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Huis, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

vitro activated peripheral blood lymphocytes (PBL) isolated at the end of the rIL-2 treatment (at the time of the AIN) was enhanced towards an autologous renal cell line cultured from the AIN biopsy specimen and an allogeneic renal cancer cell line, but not towards autologous PBL or the allogeneic melanoma cell line M14.

Case report

A 58-year-old Caucasian man with pleural metastases from renal cell carcinoma underwent left-sided nephrectomy prior to treatment with rIL-2. The nephrectomy specimen showed renal adenocarcinoma with extensive lymphocytic infiltration. No abnormalities were seen in the contiguous renal parenchyma. Continuous infusion over 24 h of 9×10^6 IU/m^2 rIL-2 (Euro-Cetus, Amsterdam, the Netherlands) was started through a central venous access for a period of 6 weeks according to a phase I protocol on an out-patient basis [27]. At the end of the 6th week of treatment, oliguria with acute renal failure developed without signs of vascular leakage syndrome. Treatment with rIL-2 was discontinued. Persistent renal failure prompted haemodialysis. A surgical biopsy specimen of the right kidney taken 2 weeks after discontinuation of the rIL-2 treatment showed normal glomeruli with a dense interstitial infiltrate consisting of lymphocytes, plasma cells and eosinophilic and neutrophilic granulocytes. This infiltrate extended into the tubules. Immunofluorescence examination with antibodies against IgG, IgM, IgA, total complement, and complement factors B1A and C1q showed no glomerular or specific tubular deposition (F. J. W. ten Kate, Department of Pathology, Erasmus University, Rotterdam, the Netherlands). Methylprednisolone pulse therapy resulted in normalization of the renal function. Four months later the patient died from rapid tumour progression. A request for autopsy was not granted.

Materials and methods

Preparation of effector cells: Peripheral blood of the patient was collected in preservative-free heparin and mononuclear cells were isolated by centrifugation on Ficoll/Hypaque density gradients and were stored in liquid nitrogen until testing. Samples were taken before and at the end of the 6 weeks of rIL-2 treatment.

After thawing, the isolated peripheral blood lymphocytes (PBL) were cultured for 5 days in medium consisting of Iscove's modified Dulbecco's medium (IMDM) with 5% pooled human serum, 100 U/ml penicillin and 100 µg/ml kanamycin and in medium with 600 IU/ml rIL-2. In order to induce T cell proliferation and activation the PBL were cultured in medium with 600 U/ml rIL-2 plus anti-CD28 (1 µg/ml) and immobilized anti-CD3 (0.5 µg/well) antibodies for 5 days [21].

The biopsy specimen of the interstitial nephritis (0.1 cm^3) was minced, homogenized and centrifuged over Ficoll/Hypaque. From the homogenate 0.9×10^6 lymphocytes and 0.1×10^6 non-lymphocytic cells were isolated. Unfortunately, the cryopreserved kidney-infiltrating lymphocytes were not viable after thawing so they could not be used as effector cells.

Because the nephrectomy specimen containing the renal cell cancer consisted merely of non-viable cells and was infected, neither tumour-infiltrating lymphocytes nor a renal tumour cell line could be cultured.

Preparation of target cells. A slowly growing cell line was cultured from the 0.1×10^6 non-lymphocytic cells isolated from the renal biopsy specimens at the time of AIN. These cells were considered to be non-malignant human epithelial cells of renal origin (autologous renal cell line, ARCL). They stained positively with the monoclonal antibodies G250 (IgG1) and RC38 (IgG1) and with monoclonal antibodies directed to HLA-class I, β_2-microglobulin and α-keratin [22, 23]. The other targets consisted of the renal cancer cell line BA, which was generated from a renal cell carcinoma of another patient, the natural-killer-cell(NK)-resistant melanoma cell line M14, the NK-sensitive erythroleukemia cell line K562 and autologous PBL sampled before rIL-2 treatment.

The cell lines ARCL, BA, M14 and K562 were cultured in medium consisting of IMDM with 10% fetal calf serum, 100 U/ml penicillin and 100 µg/ml kanamycin. The PBL were cultured in IMDM with 5% pooled human serum, 100 U/ml penicillin and 100 µg/ml kanamycin for 5 days.

Table 1. Distribution of the surface antigens of the peripheral blood effector lymphocytes before and at the end of 6 weeks recombinant-interleukin-2 (rIL-2) treatment cultured in medium alone, in medium with 600 IU/ml rIL-2, or in medium with 600 IU/ml rIL-2 with anti-CD28 (1 µg/ml) and immobilized anti-CD3 (0.5 µg/well) antibodies

Antigen	Percentage of cells positive					
	Before rIL-2			6 weeks after rIL-2		
	Medium	+rIL-2	+IL-2 +mAb[a]	Medium	+rIL-2	+IL-2 +mAb[a]
CD3	50	45	80	20	30	50
TCR$\alpha\beta$	45	45	80	15	30	55
CD4	30	25	60	15	15	40
CD8	25	25	20	10[b]	30[b]	20[b]
CD56	10	10	0	20	50	20
CD25	3	2	75	1	35	50

[a] mAb: anti-CD28 (1 µg/ml) plus immobilized anti-CD3 (0.5 µg/well)
[b] The percentage of CD8$^+$ is strongly influenced by the presence of a significant number of CD8^{dim} natural killer cells

Cell-mediated cytotoxicity assay. Samples containing 1×10^3 labelled target cells (11 µCi ^{51}Cr/10^6 cells, Amersham, Buckinghamshire, UK) were incubated in V-bottom microtiter plates with 3×10^4 effector cells in 150 µl IMDM with 0.25% bovine serum albumin. The plates were centrifuged for 5 min at 50 g and incubated at 37° C and 5% CO_2 for 4 h. After the incubation period 100 µl supernatant was collected from each well and counted in a gamma counter. All tests were carried out in triplicate. The spontaneous and the maximal release (cpm) were determined by incubation of targets in medium without effectors or in detergent (Triton-X100) respectively. The percentage specific lysis was calculated by the formula [(experimental release – spontaneous release)/(maximal release – spontaneous release)] × 100.

Immuno-phenotyping of PBL effector cells. Cell surface phenotyping of the isolated PBL was performed by fluorescence-activated cell sorter (FACScan), Becton-Dickinson) analysis using monoclonal antibodies against the surface antigens CD2 (CLB-T11.1/1, Central Laboratory of Blood Transfusion Service, CLB, Amsterdam, the Netherlands), CD3 (SPV-T3b, Netherlands Cancer Institute), CD4 (Ortho Diagnostics, Tilburg, the Netherlands), CD8 (Ortho Diagnostics, Tilburg, the Netherlands), CD25 (TB30, CLB), TCR$\alpha\beta$ (BMA 031, Kurrle R, Behring Werke, Marburg, FRG), and CD56 (Leu19, Becton-Dickinson, Etten-Leur, the Netherlands).

Immuno-phenotyping of the mononuclear infiltrate of the renal cell carcinoma and the interstitial nephritis. Immuno-phenotyping of the lymphocytes was performed on the cellular infiltrate of the nephrectomy specimen of the original renal cell carcinoma and the biopsy demonstrating the tubulo-interstitial nephritis taken 2 weeks after discontinuation of the rIL-2. Immunohistochemical assays were performed on fresh frozen sections using an indirect immunoperoxidase technique. To inhibit endogenous peroxidase activity, slides were preincubated in a H_2O_2/acetone solution (3:10000) for 10 min at room temperature. The following antibodies were used: anti-CD4 (Dako-T4, Glostrup, Denmark), anti-CD8 (Dako, Glostrup, Denmark), anti-CD16 (Netherlands Cancer Institute), anti-CD25 (Becton Dickinson) and anti-CD56 (Becton Dickinson).

Results

Characterization of the effector cells

The surface-marker profile of the PBL used as effector cells, sampled before and at the end of the 6 week rIL-2 treatment, is presented in Table 1. After 6 weeks of rIL-2

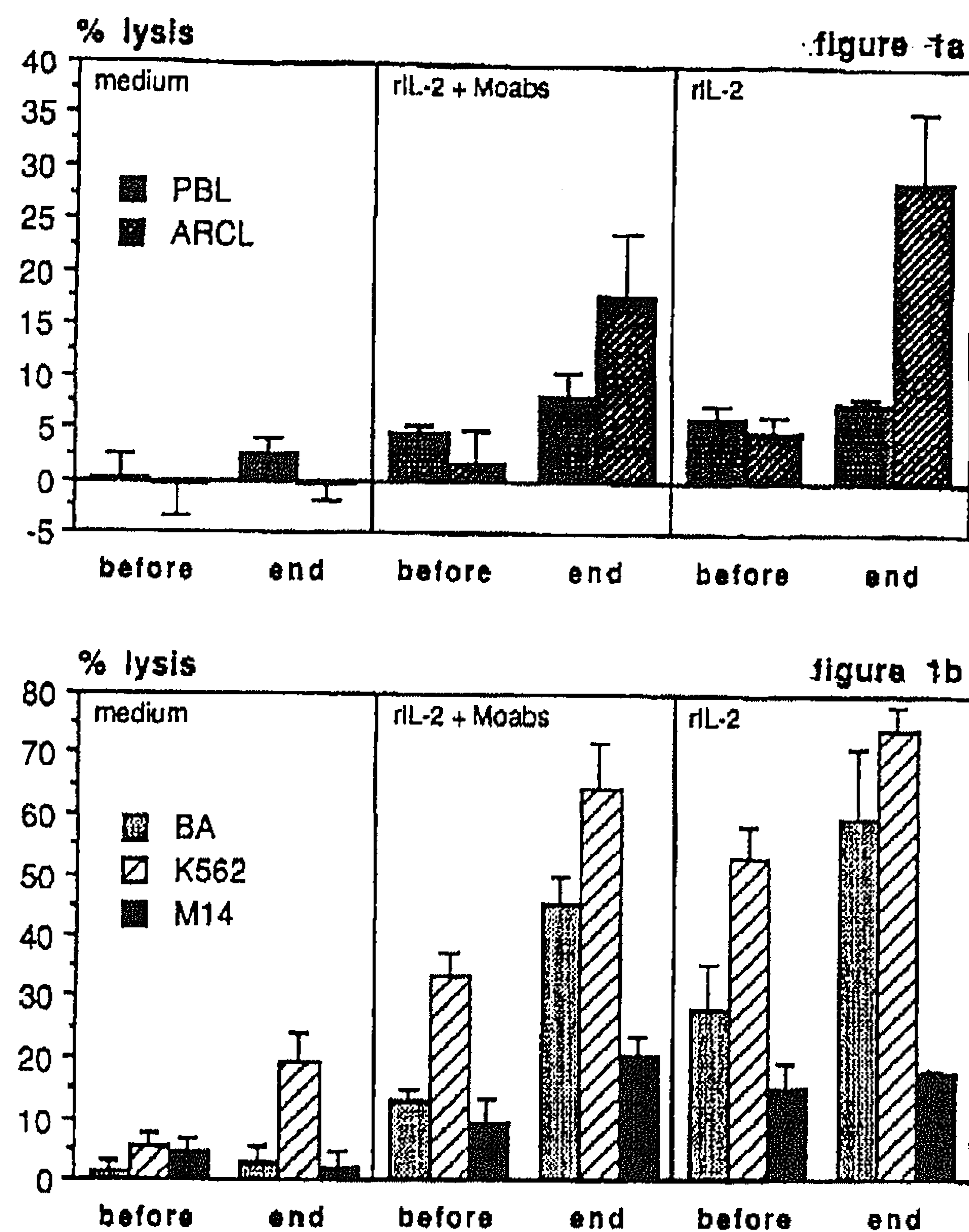

Fig. 1. In vitro cytotoxic activity (± standard deviation) of the peripheral blood lymphocytes isolated before and at the end of continuous recombinant interleukin-2 (rIL-2) treatment for 6 weeks against various autologous (**a**) and allogeneic (**b**) targets. The effector peripheral blood lymphocytes (PBL) were cultured for 5 days in medium alone, or stimulated with 600 IU/m rIL-2, with or without anti-CD28 (1 μg/ml) plus immobilized anti-CD3 (0.5 μg/well) (mAb). The effector: target ratio was 30:1. *PBL*, autologous peripheral blood lymphocytes; *ARCL*, autologous renal cell line; *BA*, allogeneic renal cancer cell line; *M14*, NK-resistant melanoma cell line; *K562*, NK-sensitive erythroleukemia cell line

treatment a dramatic decrease in the percentage of CD3+ T cells (from 50% to 20%) was observed, without significant changes in the CD4/CD8 ratio, and a small increase in the percentage of CD56+ natural killer cells.

After in vitro rIL-2 stimulation, the PBL taken after 6 weeks of rIL-2 treatment had a high percentage of natural killer cells (50%) and an increased number of CD25+ cells.

In vitro stimulation of the pretreatment PBL with rIL-2 and immobilized anti-CD3 plus anti-CD28 antibodies resulted in preferential outgrowth of CD3+ T cells, the majority (60%) being CD4+ cells. After 6 weeks of rIL-2 treatment the number of CD56+ natural killer cells (20%) was enhanced with a concomitant decrease in the percentage of CD3+ cells without changes in the CD4/CD8 ratio. The number of CD25+ cells was closely correlated with the number of CD3+ cells.

Immuno-phenotyping of the mononuclear infiltrates of the renal cell carcinoma and the acute interstitial nephritis

In the tumour-associated mononuclear infiltrate and in that of the tubulo-interstitial nephritis there was an equal distribution between the CD4+ (35/40%) and CD8+ (35/40%) CD3+ T lymphocytes and CD56+ (5/10%) cells.

Cytotoxic capacity of the effector cells

The cytotoxic capacity of the PBL, isolated before and at the end of the 6 weeks of rIL-2 treatment, towards the various target cells is depicted in Fig. 1a, b. It is demonstrated in Fig. 1a that after in vitro stimulation of the PBL with rIL-2 the cytotoxic capacity of the PBL, taken after 6 weeks of rIL-2 treatment, has evidently increased towards the autologous renal cell line (ARCL) isolated from the interstitial nephritis biopsy, but not towards autologous PBL. The cytotoxic activity of the PBL was not significantly influenced by the addition of anti-CD28 and immobilized anti-CD3 antibodies to rIL-2 in the medium.

The cytotoxic capacity of the isolated PBL towards various allogeneic targets is shown in Fig. 1b. The PBL isolated at the end of rIL-2 treatment and cultured in medium displayed evident killing of K562 (NK activity). After in vitro stimulation, the cytotoxic capacity of the PBL, isolated after 6 weeks of rIL-2 treatment, towards K562 and the allogeneic renal cancer cell line was enhanced in comparison with that of the PBL isolated before rIL-2 treatment. In contrast, there was no enhanced cytotoxicity against the allogeneic melanoma cell line M14.

Discussion

This paper describes the immunological studies performed in the first biopsy-proven case of acute (tubulo)interstitial nephritis (AIN) after treatment with rIL-2 alone in a patient with advanced renal cell cancer [8]. In the present case, no complement or antibody deposition on the tubular basement membrane (TBM) was observed, and there was no serologial evidence for complement activation or circulating anti-TBM antibodies. Therefore, we investigated whether the AIN was the result of a cell-mediated immune reaction induced by the rIL-2 treatment. We demonstrated that after 6 weeks of rIL-2 treatment the peripheral blood lymphocytes (PBL) of the patient, when stimulated in vitro, displayed enhanced cytotoxic capacity towards an autologous renal cell line (ARCL) cultured from the AIN biopsy specimen but not towards autologous PBL. In addition we observed enhanced killing of the allogeneic renal cancer cell line BA but not of the allogeneic melanoma cell line M14. These data may suggest that rIL-2 treatment in this patient with renal cell cancer led to the induction of cytotoxic lymphocytes with preferential lytic activity directed against renal cells, which may have led to immune-mediated renal injury. The question arises whether this injury is mediated by a non-specific or a specific cellular immune reaction. Essentially, non-specific and non-MHC(major histocompatibility complex)-restricted killing of targets is mediated by natural killer (NK) cells, whereas T lymphocytes exert antigen-specific MHC-restricted cytotoxicity. Recent data suggest that NK cells may also exhibit allo-antigen-specific cytotoxicity [5] and that T lymphocytes can, upon IL-2 activation, display non-specific and MHC-unrestricted cytolysis [6]. From the ex-

periments we performed, using bulk PBL that contain both T lymphocytes and NK cells, the nature of the cytotoxic reaction could not be determined with certainty.

During treatment with rIL-2, cells are generated that display non-specific and non-MHC-restricted cytotoxicity for a wide range of targets [12]. Although it was initially thought that these lymphokine-activated killer (LAK) cells should spare normal tissue, LAK cells may be cytotoxic for autologous lymphocytes and normal human cell lines including renal tubular cells [19, 24]. It may questioned whether the observed cytolytic activity of the in vitro stimulated PBL, isolated at the end of rIL-2 treatment, towards ARCL but not towards autologous PBL, may have played an actual role in the pathogenesis of AIN and does not merely represent a difference in LAK sensitivity between two different autologous targets.

Alternatively, in view of the recently demonstrated presence of tumour-specific cytotoxic T cells in renal-cell-cancer-infiltrating lymphocytes [15] and the possible role of tubular-antigen-specific cytotoxic T cells in the pathogenesis of experimental AIN [13], a specific T-cell-mediated reaction must be considered. Since renal cell carcinoma originates from the epithelial cells of the proximal tubulus and may express a number of cell-surface-associated antigens, that are shared by the various parts of the normal nephron [9, 22], a T cell response evoked against an antigen present on the tumour cells could display cross-reactivity with antigens present on the normal tubulo-interstitium. This "autoimmune" response could have been enhanced by the rIL-2 treatment leading to the cell-mediated AIN in the other kidney [17].

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