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Renal immunopathology in renal cell carcinoma *

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Summary. Signs of glomerulopathy, especially a nephrotic syndrome can occur in cancer patients, but the exact frequency of glomerular lesions is not well known in these patients. To define this frequency in a given type of malignancy we have studied the nephrectomy kidneys in 40 patients with renal cell carcinoma. Proteinuria, which was present in 7 cases, ranged from 0.15 to 1.5 g per 24 h. Reduction of the creatinine clearance greater than 50% was observed in 5 patients. Circulating immune complexes were detected in 11 of the 15 patients studied. Carcinoembryonic antigens were noted in 2 of 9 patients investigated. Research of alpha 1 foetoprotein carried out in 12 patients was always negative. HBs antigen or Hbs antibodies were detected in 6 of 29 patients studied. Light microscopic examination of the normal uninvolved kidney tissue showed obvious glomerular lesions (mesangial hypertrophy with or without deposits, with or without cell proliferation) in 7 patients (17.5%). Amyloid deposits were never observed. Immunofluorescence study revealed mesangial deposits in 35% of patients versus 5.4% of control subjects ($P < 0.0001$). These deposits included C3 and/or IgM in 13 cases, IgA and C3 in one case. No fixation was observed, neither on tubules of normal tissue nor on carcinoma lesions. This report demonstrates that glomerular deposits are usually found in approximately one third of patients with renal cell carcinoma and that these deposits are located in the mesangial areas and not in the subepithelial space as it is often observed when glomerulonephritis is expressed by clinical symptoms.

Key words: Glomerular deposits – Immunofluorescence microscopy – Renal cell carcinoma

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Introduction

Data supporting a relationship between glomerulonephritis (GN) and neoplasms have recently been accumulated (Eagen and Lewis 1977). Although subclinical glomerular immune complex deposits in patients with cancer were found in only 1.5% of patients with solid tumors (Sutherland et al. 1974) Pascal et al. (1976) found, using electron-microscopy, electron dense glomerular deposits in 55% of autopsied cancer patients. By immunofluorescence microscopy, we have observed glomerular deposits in 17% of patients who had died with carcinoma (Beaufils data to be published). In our study, glomerular deposits are more frequent (27%) in patients with digestive carcinoma. Since the frequency of subclinical GN was perhaps subordinate to the localization of the carcinoma it appeared interesting to study the occurrence of immune deposits in a group of patients affected by the same localization of carcinoma, especially since only three reports have studied this aspect: two in a group of patients with broncogenic carcinoma (Davis et al. 1980; Ozawa 1978) and one with renal cancer (Holm et al. 1982). Therefore in the present study the normal and tumoral kidney from 40 patients with renal carcinoma were investigated for the presence of glomerular deposits.

Patients and methods

Fourty consecutive patients admitted for surgical removal of renal carcinoma, were examined. Twenty-nine were males, and 11 females. Their age ranged from 26 to 79 years (mean 61 years). None except one with chronic hepatitis had concomitant diseases known to be associated with the formation of circulating immune complexes. Pre-operative blood pressure, 24 h urinary protein excretion and creatinine clearance were measured. The patients were qualified as "hypertensive" only in the presence of a blood pressure readings of 140/90 mm Hg or greater in patients 55 years of age or younger; patients above the age of 55 required blood pressure reading of 150/100 mm Hg or greater to qualify as "hypertensive". The following immunologic investigations were usually performed, but in some cases not all the tests could be completed. Measurement of ASO titers ($N < 200$ U AS/ml); detection of hepatitis B surface antigen (HBs Ag) and of antibodies to HBs Ag (anti-HBs) and/or to the Dane bodies (anti-HBc) by passive hemagglutination or by radioimmunological assay. Detection of anti-nuclear antibodies, alpha-1-foetoprotein and carcinoembryonic antigen, and research of the rhumatoid factor by Waaler-Rose and latex tests. Circulating immune complexes were assayed in sera by precipitation with polyethylene glycol (Grangeot and Pillot 1975; Gluckman et al. 1978). The study of serum immunoglobulins (IgA, IgG, IgM) and levels of complement fractions (C3, C4, C3PA) were performed by radial immunodiffusion and the total hemolytic complement activity (CH 50) was tested as well.

Kidneys from all the patients were obtained at the time of nephrectomy. Parts of normal tissue were cut off in a normal zone as far from the tumoral tissue as possible. Renal tissue was stained with Masson's trichrome, haematoxylin eosin, periodic acid Schiff, Wilder reticulin, and specific staining for amyloidosis (thioflavine T and Congo red with polarization) for light microscopy. Carcinoma stage was scored according to Robson et al. (1969). 55 control kidneys of subjects who died from various causes mainly cardiovascular diseases and without past history of wellknown diseases with immune complex GN (i.e. cirrhosis, endocarditis, systemic lupus erythematosus) were included in this study. These control cases were matched by age and sex with the patients. For immunofluorescence microscopy, the renal fragments were snap-frozen in liquid nitrogen, cut and then covered with antisera. Antisera specific for human IgA, IgG, IgM, C3, albumin (goat serum Hyland Laboratories) and C1q, C4, fibrinogen, kappa, lambda, hepatitis B associated surface antigen (rabbit serum Behringwerke Laboratories) were used in each case. These antisera gave no fluorescence with normal tissue.

Results (Tables 1 and 2)

Clinical findings. Patients were examined for the usual symptoms of renal carcinoma. However the diagnostic triad of hematuria, flank pain and palpable mass was never observed. Of the 40 cases studied, 12 patients were found to have had hypertension pre-operatively. Of these 12 hypertensive patients, 2 (cases 5, 17) presented severe hypertension. Two patients (cases 4, 16) were found to have diabetes mellitus. The median time from the initial symptoms to nephrectomy was 13 months (a few days to 9 years). Nephrectomy was performed in 22 patients during the first 6 months after the initial symptoms. 26 of the patients were followed after nephrectomy: 2 died during the postoperative period, and one 7 months after nephrectomy; 23 patients were investigated again 1–18 months (average 12 months) later: 15 were well, 7 had a local or metastatic relapse. Satisfactory postoperative blood pressure was obtained in the 2 patients with severe hypertension, one spontaneously, other with treatment.

Immunological results. ASO titers were normal in 19 patients, elevated in one (300 U AS/ml). Antinuclear antibodies and rhumatoid factor were absent in 18 patients, present in one but with low levels. The research of alpha-1-foetoprotein was negative in all the 12 patients tested. Carcinoembryonic antigen was found in 2 of 9 patients, HB virus markers were found in 6 of 29 sera tested. Circulating immune complexes were detected in 11 of the 15 investigated sera: they included either IgG alone (2 cases), or IgG-IgM (3 cases), or IgG-IgM with complement (3 cases), or IgG with complement (1 case), or IgM with complement (2 cases). Total hemolytic complement activity was low in 2 of 15 sera studied; levels of complement fractions were reduced in one case, normal in the 30 other cases. Serum immunoglobulins levels were abnormal in all the 19 patients tested, demonstrating global hypergammaglobulinemia in 3 cases, increase of IgA and/or IgM in 12 cases, and decrease of IgG and/or IgA in 6 cases.

Renal anomalies. Proteinuria was present in 7 patients and ranged from 0.15 to 1.5 g/24 h. In one patient, proteinuria was absent at the time of nephrectomy but was present (3.50 g/24 h) 7 months later without any sign of tumoral relapse. The renal function was reduced in 10 cases, but the creatinine clearance was less than 50% of the normal range in only half of them.

Pathological features. (Figs. 1, 2, 3, and 4)

Study of the carcinoma: the tumour was located in the right kidney in 22 patients, the upper pole of the kidney in 20 cases, the lower pole of the kidney in 10 cases, it was median in 9 cases and was extensive in the last case. The stages of renal carcinoma were as follows: stage I in 12 cases (30%), stage II in 9 cases (22.5%), stage III in 14 cases (35%), stage IV in 5 cases (12.5%). By light microscopy, renal carcinoma included clear cells in 36 patients (90%), while sarcomatoid carcinoma was noted in 2

Table 1. Analysis of cases

Case N°	Pu g/24 h	Cr. Cl. ↘ 50%	C.I.C	HB	C.E.A	Stage of tumor	Glom.	T.I.	V	IF
1	0.50	−	ND	Ab	Neg.	II	F	+	+	−
2	0.60	−	ND	ND	ND	IV	O	O	O	−
3	0.45	−	Neg.	Neg.	ND	III	M	OED	O	IgM
4	1.30	+	ND	Neg.	ND	IV	H.C	++	++	C3
5	0.15	−	ND	Neg.	Neg.	I	O	++	+	−
6	0.65	−	ND	ND	ND	I	F	+	O	−
7	1.50	−	Pos.	Neg.	ND	II	O	+	++	−
8	−	−	ND	Neg.	ND	III	H, C	+	+	−
9	−	−	ND	ND	ND	III	MC	O	+	−
10	−	−	Pos.	Neg.	ND	III	O	INF	+	−
11	−	+	ND	Ab	Pos	I	O	++	++	−
12	−	−	ND	Neg.	Pos.	III	MC	+	+	C3
13		−	ND	Neg.	ND	III	M	INF	++	IgM
14		−	ND	ND	ND	I	F	+	O	IgMC3
15	−	−	ND	ND	ND	II	O	+	+	−
16	−	−	Pos.	Neg.	ND	III	O	O	+	−
17	−	−	Pos.	Ag	ND	I	F	+	+	−
18		−	ND	ND	Neg.	III	M	+	++	C3
19	−	−	ND	ND	ND	I	O	O	++	−
20	−	−	Pos.	Neg.	ND	IV	O	O	O	−
21	−	+	ND	ND	Neg.	I	F	+	+	−
22	−	−	Neg.	Neg.	ND	I	FM	+	+	−
23	−	−	Pos.	Ag	ND	IV	O	+	+	−
24	−	−	Pos.	Neg.	ND	III	HD	++	O	C3
25	−	+	ND	ND	ND	II	O	+	++	−
26	−	−	ND	ND	ND	II	O	O	+	−
27	−	−	Pos.	Neg.	ND	I	FM	+	O	IgMC3
28	−	−	Neg.	Neg.	ND	III	MC	O	O	−
29	−	−	ND	Neg.	ND	IV	M	+	++	IgMC3
30	−	−	ND	Neg.	Neg.	I	O	O	O	−
31	−	−	ND	Neg.	ND	III	F	+	+	−
32	−	−	Pos.	Neg.	ND	III	M	+	O	−
33	−	−	Neg.	Neg.	ND	II	O	+	O	−
34	−	−	ND	Neg.	ND	II	O	O	O	−
35	−	−	ND	Neg.	Neg.	II	M	+	+	IgM
36	−	−	Pos.	Neg.	ND	III	M	++	+	IgMC3
37	−	−	ND	ND	ND	II	O	O	++	IgM
38	−	−	Pos.	Neg.	ND	I	H	O	+	IgAC3
39	−	−	ND	Ab	Neg.	III	O	O	O	−
40	−	+	ND	Ag	ND	I	M, F	++	++	IgMC1q

Abbreviations: Pu = Proteinuria (− no proteinuria); Cr. Cl. = Creatinine clearance; C.I.C. = Circulating immune complexes; HB = Research of serological HB virus markers; ND = not done; Neg = negative; Ag = positive for antigen: Ab = positive for antibody; C.E.A. = Research of carcino-embryonic antigen; ND = not done; Neg = negative; Pos = positive.

Glom = Glomerular lesions; O = absence; F = fibrosed glomeruli (more than 10%); M = mild and irregular mesangial prominence; H = obvious mesangial hypertrophy; C = mesangial hypercellularity; D = mesangial deposits.

II = Tubulo interstitial lesions (O to ++); OED = oedema; INF = interstitial inflammatory cells.

V = Vascular lesions (O to ++).

IF = Immunofluorescence on glomeruli; − = no deposit

Table 2. Biological, immunological and immunopathological data

Results	Protein-uria	Immune com-plexes	HB virus markers	Carcino embryonic antigen	Immunofluorescence		
					Non tumoral kidney		Tu-mor
Positive	7	11	6	2	(C3) 4 (IgM) 4 (IgM-C3) 4 (IgM-C1q) 1 (IgA-C3) 1	14 (35%)	0
(%)	(20,6)	(73,3)	(20,7)	(22,2)			
Negative	27	4	23	7	26		40
Number of investigated patients	34	15	29	9	40		40

cases, undifferentiated carcinoma in 1 case and papillary cystadenocarcinoma in the last case. Amyloidosis was never detected.

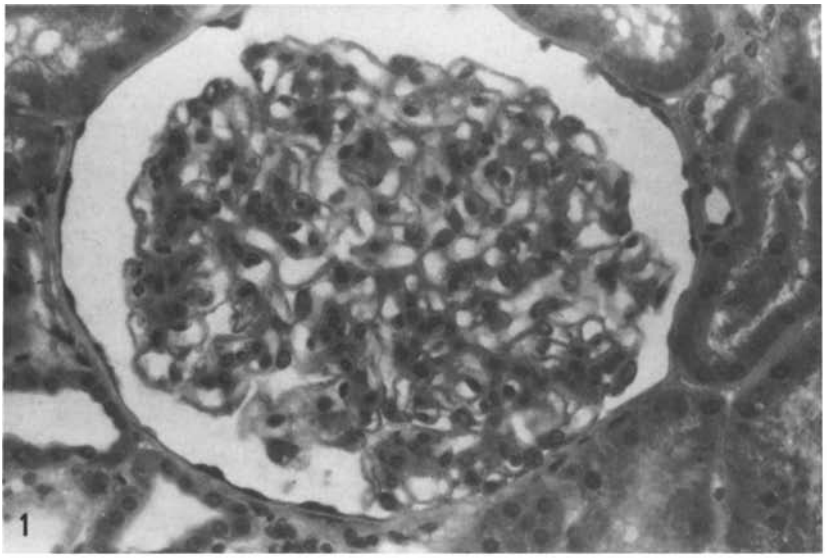
– Study of the normal kidney tissue: no lesion was observed in 5 patients. The 35 others patients had glomerular lesions and/or interstitial and tubular changes and/or vascular lesions. Amyloidosis was never detected by specific staining.

+ Glomerular lesions were noted in 25 patients: extensive (more than 10% of glomeruli) hyalinisation in 9 instances, mild increase of mesangial matrix in 13 cases and in 7 patients the mesangial matrix was widely enlarged with fibrinoid deposits in 2 cases and/or mild increased cellularity in 5 cases.

+ Tubulo-interstitial lesions were present in 28 patients: few interstitial foci of acellular fibrosis with tubular atrophy in 19 patients, more of the same lesions in 6 patients. Interstitial inflammatory cells were observed in 2 patients. In the last case an acellular interstitial edema with flattened tubular epithelium was undoubtedly secondary to a complete neoplastic thrombosis of the renal vein.

+ Damaged vessels were observed in 27 patients. The lesions consisted of intimal thickening with reduplication of the internal elastic lamina, or hyaline deposits. Ten patients had greater than 50% of their vessels damaged; 6 of them were aged 70 or more and 2 were being treated for arterial hypertension.

– Immunofluorescence microscopy: Glomerular deposits were observed in 14 patients. In all, the fluorescence pattern was granular, diffuse, present in all glomeruli, but in most of them, only a few small granules were seen. Deposits were located only in mesangial areas in 10 patients, and were observed in mesangium and along some basement membranes in 4 patients (cases 13, 27, 36, 40). Deposits of IgM were demonstrated in 9 patients: they were isolated in 4 instances, associated with deposits of C3 in 4 cases or C1q in 1 case. Isolated deposits of C3 were seen in 4 patients. In the last patient, mesangial deposits of IgA, C3 were detected. Thrombi in glo-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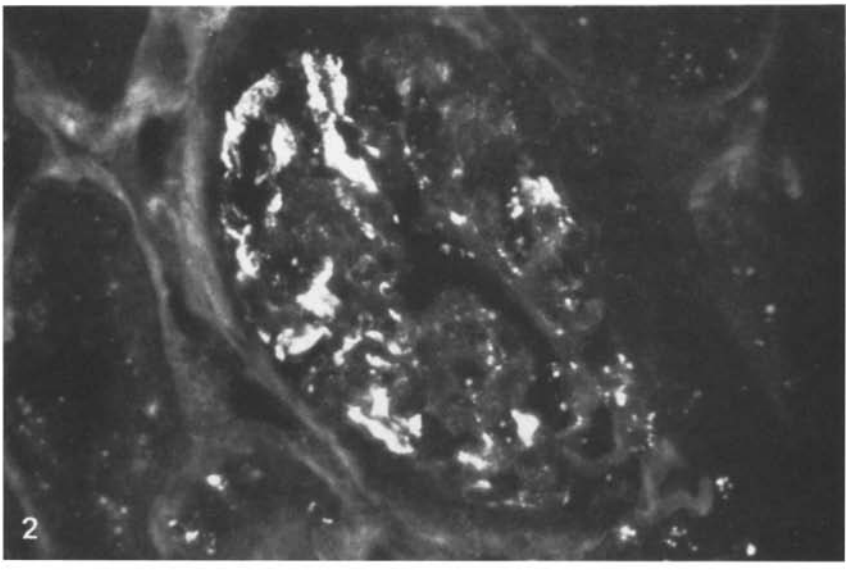
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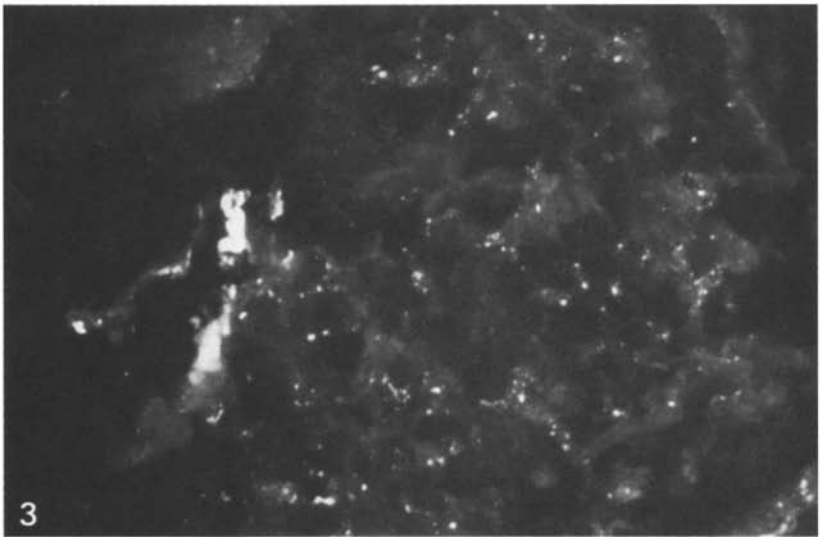
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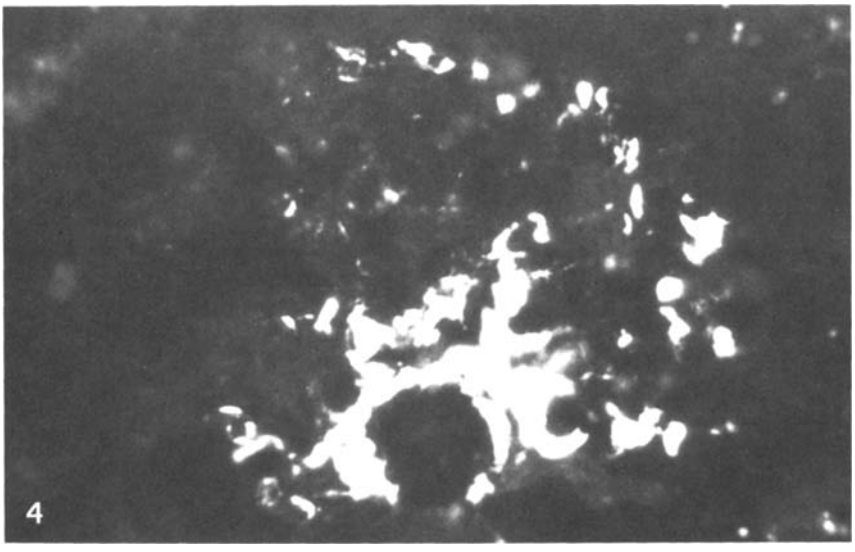

Fig. 4. Mesangial deposits of IgA. Fluorescent micrograph of a section stained with anti-IgA. Case 38 (× 200)

merular capillaries were revealed by anti fibrinogen serum in 6 patients. Deposits of C3 were observed in some arteriolar deposits. No fluorescence was obtained with the antiserum specific for hepatitis B associated surface antigen. No deposits were noted on the tubules or on the tumoral tissue.

– Immunofluorescence microscopy of control kidneys: only 3 out of 55 kidneys (5.4%) stained positively, one with IgM deposits and two with C3 granules (Beaufils to be published).

Discussion

Numerous publications collected by Eagen and Lewis (1977) relate case reports of cancer patients displaying a nephrotic syndrome. The latter is often the clinical expression of a membranous GN, but all types of GN have been described. Thus, in patients suffering from renal cell carcinoma and nephrotic syndrome, cases of membranous GN (Denis et al. 1978; Grossman and Croker 1978; Kerpen et al. 1978), of minimal changes (Mc Canse et al. 1975; Dupond et al. 1980), of mesangiocapillary GN (Lee et al. 1966), of GN with epithelial crescents (Hopper et al. 1976) have been published. In these patients with renal cell carcinoma, the nephrotic syn-

Fig. 1. Mesangial hypertrophy with irregular hypercellularity. Light photomicrograph of a Masson's trichrome stained section. Case 8 (× 150)

Fig. 2. Mesangial and parietal deposits of IgM. Fluorescent micrograph of a section stained with anti-IgM. Case 13 (× 200)

Fig. 3. Mesangial granules of C3. Fluorescent micrograph of a section stained with anti C_3 Case 4 (× 300)

drome can also be secondary to amyloidosis (Couser et Colvin 1980; Tard et al. 1980; Pras et al. 1982; Mignon et al. 1982) which occurs in 1 to 5% of patients in the course of renal cancer (Ask-Upmark 1940; Berger and Sinkoff 1957; Penman and Thomson 1972).

If reports of carcinoma with nephrotic syndrome are numerous, the publication regarding the frequency of glomerular deposits in patients with cancer are less frequent (Sutherland et al. 1974; Pascal et al. 1976; Helin et al. 1980; Beaufils to be published). Glomerular changes are described in some non-nephrotic patients with renal cell carcinoma, that are especially located in the mesangium (increase of mesangial matrix, mild hypercellularity) with deposits of C3 and immunoglobulins (Ozawa et al. 1975; Cronin et al. 1976; Pascal et al. 1976). In a recent work (Holm et al. 1982) immunofluorescence examination indicated the occurence of glomerular immune deposits in 14 of 16 non tumoral tissue: IgG, IgM and C3 were demonstrated in most patients, IgA in three patients.

We report here a microscopical and immunopathologic study of normal and tumoral kidney tissue of 40 patients who underwent nephrectomy for renal cell carcinoma. These 40 patients have clinical and pathological features that may be compared to the other cases in the literature (Berger and Sinkoff 1957; Chisholm and Roy 1971; Bennington 1973; Cukier et al. 1979). No amyloid deposit was detected in our 40 nephrectomized kidneys, perhaps because of the precocity of the examination in the course of the disease. Glomerular deposits are present in 35% of patients versus 5.4% of control subjects ($P < 0.0001$). We did not observe any correlation between the presence of glomerular deposits and the stage of tumor's extension, the duration of illness before nephrectomy, the presence of arterial hypertension or of diabetes. The deposits which are mainly located in mesangium are composed of IgM in 9 patients, of C3 in 4 and of IgA in one. The latter patient had recurrent hematuria for 9 years before the discovery of renal tumor. Without the demonstration that IgA deposited in glomeruli had anti-tumoral specificity, we can no more link these immune deposits to a para-neoplastic GN than to a coincidental Berger's disease.

The question of whether the immunoglobulin deposits observed in our patients represent immune complexes or proteins which have been secondarily trapped in injured tissue is impossible to answer with certainty. Nevertheless the presence of IgM and/or C3 in all glomeruli contrary to usual patchy deposits of IgM in cases of pyelonephritis (Beregi et al. 1974) and the presence of soluble immune complexes in some of our patients suggest that the deposition of immunoglobulin and complement in patients with renal carcinoma have a pathogenic significance.

Since soluble immune complexes are frequent in plasma of patients with neoplasms (Rossen et al. 1977; Teshima et al. 1977), glomerular injury could develop in some patients from deposition of these complexes. In fact, tumor antigen and/or antibodies to tumor antigen have been demonstrated in the glomerular immune deposits in some patients (Lewis et al. 1971; Couser et al. 1974; Weksler et al. 1974; Olson et al. 1979). Other possible antigen-antibody systems might be operative in cancer patients. Thus, a CEA-anti-

CEA immune mechanism was suggested (Costanza et al. 1973) and then demonstrated in some reports (Pascal and Slovin 1980; Wakashin et al. 1980). This immune response might mediate a GN in renal cancer patients since the level of CEA is often elevated in these patients (CHU et al. 1974) as we have verified in 2 of the 9 patients tested. Ozawa et al. (1975) suggest the role of an autologous non-tumor antigen, renal tubular brush border antigen, in the pathogenesis of GN with renal cell carcinoma. This renal carcinoma does originate from proximal tubular epithelium and may produce a proximal tubular antigen (Carter 1968; Tannenbaum 1971). However antibody to tubular brush border antigen was not demonstrated in the glomerular eluate in a case with renal cell carcinoma and a nephrotic membranous GN (Kerpen et al. 1978). Evidence for the role of nuclear antigens (Higgins et al. 1974) and viral antigens (Hyman et al. 1973; Oldstone et al. 1974; Berthoux et al. 1976) also exists. With regard to the possible role of viral antigens, the high percentage of HB virus serological markers in our patients as compared with a population of blood donors (Crouzat-Reynes et al. 1982) requires confirmation by other investigators.

We are still far from understanding why only a small fraction of cancer patients with glomerular immune deposits have clinical renal disease. Nevertheless, the recognition of the prevalence of glomerular deposits in the kidneys of cancer patients may help to identify some causal relationship between the neoplastic condition and the respective glomerular lesions.

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Note from the managing editors

This paper was not accepted without hesitation. We would have preferred the authors evidence to have been confirmed by electron microscopy.

However, serious doubts are not justified, as fluorescence microscopy is a *comparatively* more sensitive and reliable method in this case. We hope that the study will receive the attention it deserves.