A TWO-HEADED COIN: RENAL DISEASE AND NEOPLASMS

(or: "Heads - you win; tails - I lose)

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Medical Grand Rounds

U. T. Health Sciences Center at Dallas

October 8, 1981

The kidney is involved directly or indirectly with neoplasia in several ways. The most frequently encountered are metabolic consequences of diverse tumors and the anatomic complications of neoplasms directly invading or impinging on the urinary tract (Table I).

Table I RENAL FUNCTIONAL SYNDROMES ASSOCIATED WITH DISTANT NEOPLASM

A. Due to circulating hormones or minerals

1. SIADH
2. hypercalcemia
3. hyperuricemia

B. Due to obstruction

1. polyuria
2. renal failure (partial obstruction)
3. anuria (complete obstruction)

This presentation will not deal with either of these major categories of tumor-related renal disease. Instead, I will focus on (1) renal disease which is induced either by immunological mechanisms or perversions of immune systems complicating neoplasia, and (2) neoplasia occurring in association with, or as apparent complication of, chronic renal failure. I want to explore with you the generalities of present information regarding participation of immunopathogenetic mechanisms in these broadly disparate circumstances (Table II). It is not my intent to discuss primary renal malignancy *per se*; also excluded are rare and anecdotal syndromes.

Table II RENAL DISEASE AND MALIGNANCY: IMMUNOLOGIC SYNDROMES AND RELATIONSHIPS

A. Renal complications of extra-renal malignancy

1. glomerulonephritis
2. nephrotic syndrome
3. complications of multiple myeloma
4. glomerulopathies of dysproteinemias and cryoglobulinemia

B. Malignancies complicating chronic renal disease

1. analgesic abuse: transitional cell carcinoma of urinary tract
2. cystic transformation and tumors in dialysis kidneys
3. uremic immunosuppression and spontaneous malignancy

A. Cancer as a cause of several renal diseases:

In broad terms our understanding of humoral nephritogenic mechanisms has been broadened to three principal processes: (1) Antibody directed to intrinsic

structural components associated operationally with the glomerular basement membrane (GBM), anti-GBM antibody, (2) injury resulting from passive deposition of preformed, circulating, soluble immune complexes, and (3) binding of circulating antibody to disparate and discrete, geographically distinct antigens associated with the glomerulus but distinct from the GBM. These latter antigens may be native glomerular antigens or acquired antigens and lectins. Although I shall not discuss the possibility again, these same humoral mechanisms apply generally to tubulointerstitial nephritis.

1. Crescentic glomerulonephritis: Although not precisely synonymous, crescentic glomerulonephritis is the histologic counterpart of severe glomerular injury; rapidly progressive glomerulonephritis, its functional counterpart, is marked by obvious renal impairment, usually progressing to oliguria, anuria, or end-stage disease in a relatively short interval. Production of glomerular crescents involves proliferation within Bowman's capsule of cells extrinsic to the glomerular capillary wall. These usually are thought to be parietal epithelial cells and/or wandering macrophages from the circulation (extracapillary proliferation). These crescents involve from 20-100% of the glomeruli examined. Because crescentic glomerulonephritis is not a common clinical problem, most published series tend to be relatively small. Nonetheless, it would seem that 7-8% of patients presenting with rapidly progressive glomerulonephritis have a previously undiagnosed visceral neoplasm. Few reported cases have been studied immunopathologically (1-4) and there is no uniformity to the data. Presumably, crescentic glomerulonephritis may be induced by any of the humoral mechanisms, with the proviso that the renal injury be sudden and severe. The role of cell-mediated immunity in such lesions is an unresolved issue for which there are not strong data at present.

2. Nephrotic syndrome: Nephrotic syndrome has been the most frequently detected glomerulopathy in patients with neoplasms. The first clinical report is attributed to Lee and co-workers (5), who reported that 10.9% of 101 patients evaluated for nephrotic syndrome unassociated with other systemic disease (e.g., diabetes mellitus, etc) were found to have cancer in the course of their illness. Since that time numerous reports and reviews (6,7) have been published. Two major pathogenetic entities cause nephrotic syndrome in these patients: (a) membranous nephropathy, and (b) nil lesion.

Membranous nephropathy: This is defined histologically by the presence of electron-dense sub-epithelial deposits in all glomeruli (epimembranous deposits), thickened glomerular capillary walls by light microscopy, and diffuse, generalized immunoglobulin deposits and other immunoreactive proteins by immunofluorescent examinations. Although this has been regarded as a prototypical immune complex-mediated glomerular disease, the precise mode of its induction can vary in experimental animals. In the animal with chronic serum sickness nephritis from bovine serum albumin administration membranous nephropathy results from the deposition of circulating immune complexes (8). However, membranous nephropathy also can be induced by passive administration of preformed antibodies which bind to anatomically disparate proteoglycen binding sites located principally in the lamina rara externa (9). Hence, two different mechanisms can cause the same lesion.

Membranous nephropathy is the identifiable nephropathy usually encountered with carcinomas (5,7). Eagen and Lewis have summarized many of the most careful

immunopathologic studies from the perspective of possible antigen-antibody systems involved (Table III).

Table III POTENTIAL NEPHRITOGENIC ANTIGEN-ANTIBODY SYSTEMS WHICH MAY OPERATE IN PATIENTS WITH NEOPLASIA (Eagen & Lewis)

tumor-associated antigens
re-expressed fetal antigens
viral antigens
autologous non-tumor antigens

In the strictest sense, stringent criteria should be applied to allow confidence that these nephropathies are indeed related causally to the neoplasms; in most cases these criteria have not been explored so convincingly as in experimental animal systems (10). Nonetheless, the weight of data suggest strongly that there is an immunologically mediated relationship between the tumor and glomerulonephropathy (11,12). There are no data presently available which compel a choice between either of the two immunopathogenetic mechanisms - circulating immune complexes or immune complex formation in situ.

This relationship has been tested in other ways. Cancer patients have been demonstrated to have measurable amounts of apparent circulating immune complexes. Moreover, consecutive patients with malignancies underwent renal biopsies in efforts to detect subclinical glomerular disease (13). While no patient had histologically apparent glomerulonephritis, glomerular electron-dense deposits were seen by electron microscopy in 11 of 24 technically adequate specimens; 8 of the 11 patients also had at least one positive test for circulating immune complexes.

Clinically, cases of nephrotic syndrome associated with carcinomas usually have not had a favorable outcome. Whereas several patients have remitted their proteinuria after successful resection of tumor, most have died in a relatively short time from widespread metastases or complications of therapy.

Nil lesion or minimal change disease (lipoid nephrosis): Nephrotic syndrome (NS) accompanied by no distinctly abnormal histomorphology by light, immunofluorescence, and electron microscopy (EM) is an enigmatic description of ignorance. The usual cause of nephrotic syndrome in otherwise healthy children and a common cause of NS in adults, nil lesion is also the most common histologic pattern found in NS associated with Hodgkins Disease and lymphomas. Glomerular changes seen and considered acceptable in "nil disease" are widespread effacement and fusion of glomerular epithelial cell foot processes. Despite good experimental evidence that integrity of foot process organization is an important factor maintaining discrimination of glomerular filtration, conclusive data are not at hand which clearly show whether the foot process abnormality dectected in these patients is cause or effect of the proteinuric state. Nevertheless, the frequent occurrence of nil lesion nephrotic syndrome in otherwise healthy children, its predictable remission in response to steroids and cytotoxic agents, and the absolute lack of markers of humoral immune participation all have suggested to many that this is a chemical or electrostatic lesion of the glomerular filter. Alternatively, Shalhoub has suggested that this may be a distant effect of altered

lymphocyte function mediated by a lymphokine or secretory product (14). There are no data presently supporting this latter hypothesis.

Nonetheless, nil lesion NS is the usual glomerulopathy which occurs in Hodgkins Disease. Moreover, it tends to be predictably responsive to treatment, in parallel with tumor responsiveness, and may be a herald or accompaniment to relapse. Remissions of N.S. apparently are induced as readily by radiotherapy as by chemotherapy. As might be inferred from the foregoing, immunohistochemical staining of nil lesion kidneys in Hodgkins Disease shows no markers of ongoing humoral immunopathogenesis. On the other hand, glomerulopathies complicating non-Hodgkins lymphoma and chronic lymphatic leukemia are less predictably nil lesion.

3. Nephropathies associated with Multiple Myeloma (M.M.): Renal disease is a common complication of M.M., reflected in tubular syndromes, renal insufficiency, characteristic morphologic changes, and frequent death due to renal failure (15). Probably 50-70 percent of patients with M.M. excrete into their urine abnormal amounts of homogeneous immunoglobulin light chain component, i.e., Bence-Jones protein. Normally, these proteins characteristically are filtered by the glomerulus and reabsorbed and catabolized by the proximal renal tubule cells. In M.M., presumably because of the enormous load or some characteristic quality of the monoclonal protein filtered, a variable fraction of the filtered load may not be reabsorbed, and is excreted in the final urine (16,17). Rarely is a whole monoclonal Ig molecule excreted into the urine; such instances, as well as unselective proteinuria, probably reflect glomerular disease. Whereas multiple myeloma is usually marked by a complete monoclonal immunoglobulin protein in the serum, with or without urinary light chain excretion, as many as 25% of patients (18) may have only monoclonal light chain urinary product with or without serum light chains detectable (Light-chain myeloma). Renal failure is frequent in this latter group of patients.

The commonest complication of M.M., and the classic lesion morphologically, has been termed "myeloma kidney" or "cast nephropathy". It is characterized by eosinophilic, refractile casts in the distal nephron, giant cell reaction formation, and tubular atrophy. Pathogenesis of this lesion has been attributed to intraluminal precipitation of the monoclonal protein, obstruction, fracture of tubule basement membranes and entry of macrophages from the interstitium with resultant formation of giant cells (19,20). The presence in these casts of other serum proteins as well as cellular debris and Tamm-Horsfall protein have suggested that coprecipitation of these proteins, perhaps due to their high concentration, urinary acidity, or protein charges may be operative. Experimental induction of similar lesions in mice injected with purified light chains suggests, however, that the concentration and charge characteristics of monoclonal protein relative to urinary acidity are most important (21). Not all casts contain the putative monoclonal light chain.

Renal amyloid occurs as a complication most commonly of so-called light chain myeloma, usually in association with λ light-chain disease, although Stone and Frenkel's experience (18) showed no such λ preference.

Fanconi Syndrome, characterized by multiple proximal renal tubule reabsorptive defects, with or without tubular acidosis, has been described numerous times to precede overt recognition of an underlying myeloma (22). It seems always to

occur in association with pathological monoclonal light chain proteinuria, usually κ. In specimens from many of these patients crystals have been seen in tubule cells, presumably the pathologic protein.

Whereas proliferative glomerulonephritis has been described extremely rarely in M.M. (23), another relatively uncommon nodular glomeropathy has received much attention recently, and has come to focus attention to a new dimension regarding the pathophysiology of renal failure in M.M. Randall and co-workers (24) described 2 patients, one with M.M., who had progressive renal failure and multisystem disease. Their kidneys at post-mortem examination had nodular glomerular changes, thickened glomerular and tubular basement membranes, and there were widespread tissue deposits in blood vessel walls, myocardium, gastrointestinal tract, and other organs - all of which stained only for kappa chains. Since then there have been several reports of nodular glomerulopathy associated with kappa chain deposition. Most of these reports have described prominent glomerular changes, often with subendothelial or mesangial deposits or electron-dense transformation of the GBM; In most cases only κ chains have been demonstrated in the lesions (25). There are three important characteristics of note in these cases: (1) whereas most cases have been patients with M.M., in several patients an overt plasma cell dyscrasia has not been demonstrable pathologically; (2) this syndrome requires immunohistochemical stains for light chains to make the diagnosis; (3) prospective studies (26) have demonstrated that tissue deposition of free light chains may be more common than recognized heretofore - and that while glomerular changes may be more conspicious, the light chain deposits around tubules, and transformation of TBM, may be more common and important.

The pathogenesis of this light chain glomerulosclerosis is not defined. Presumably it is caused by persistent blood levels of light chains which are peculiarly prone to precipitate in tissues because of chemical or charge affinities, and may not be readily excreted because of polymeric or configurational variables. Several cases have been described of so-called "non-secretory" myeloma in which Bence-Jones proteinemia or proteinuria could not be demonstrated by usual techniques. Laboratory studies have suggested, however, that this group of dysproteinemias may be marked by production of chemically anomalous light chains (27). Moreover, this light chain deposit disease may be a counterpart to AL amyloid, in which the kappa chains have an intrinsic resistance to proteolysis and amyloidogenesis, or in which tissue cofactors are deficient for amyloidogenesis. It is not clear that this syndrome of glomerular nodular sclerosis, renal insufficiency and tubular basement membrane transformation is caused by kappa light chain deposits only (28), but that is the principal description to date.

4. Glomerulopathies complicating other monoclonal dysproteinemias and cryoglobulinemia: In contrast to multiple myeloma, the monoclonal protein produced in Waldenströms macroglobulinemia is IgM, and clinical renal disease is much less common. The usual histologic abnormality seen is apparent intraluminal capillary deposits in occasional or numerous glomeruli. These deposits sometimes are small, but often may be so large as to occlude the glomerular capillary. Electron microscopically they are subendothelial, and usually stain immunohistochemically for the circulating monoclonal protein. Rarely is there apparent glomerular hypercellularity or inflammatory response to these masses (thrombi or coagula), and Morel-Maroger (29, 30) and others have suggested that they are physical precipitates caused by steric variables, and the hydrodynamic features

of glomerular filtration - such as increasing protein concentrations achieved along the length of the filtration surface. A variety of miscellaneous, albeit less common, glomerular abnormalities have been described including amyloid and apparent nil lesion nephrotic syndrome. Several reports suggest that substantial improvement or frank remission of NS may follow chemotherapy of the macroglobulinemia.

In further contrast to myeloma, despite frequent excretion of light chains in these patients, tubular casts and "myeloma kidney" are seen but rarely, but a cellular infiltrate apparently typical of the proliferating neoplasm may be seen in focal areas of the kidney. The reason that casts are not seen is not clear, but may have to do with the apparently lesser quantitative excretion of light chains in these patients.

Cryoglobulinemia: Brouet et al (31) have suggested designating monoclonal cryoglobulins as type I, mixed cryoglobulins with a monoclonal component as type II, and mixed, polyclonal cryoglobulins as type III. In general, cryoglobulins in serum of patients with multiple myeloma and lymphoproliferative diseases are type I or II, and present in relatively large amounts when they occur. Conversely, most cases of type I and II cryoglobulins occur in patients with M.M. and lymphoproliferative disorders, although some may be caused by benign monoclonal gammopathy or essential mixed cryoglobulinemia. As discussed before, glomerular lesions are uncommon in M.M. and tubular disease is recognized more frequently, whereas bland glomerular changes are characteristic of the renal lesion of macroglobulinemia. On the other hand, proliferative and membranoproliferative (mesangiocapillary) glomerulonephritis have been described numerous times in cases of type I and II cryoglobulinemia. This nephritis clinically may be acute, severe, cause renal failure, and resolve despite persistence of the cryoglobulinemia, or it may persist as a chronic glomerulonephritis.

Pathologically there tends to be a striking glomerular endocapillary proliferation, often with necrosis and polymorphonuclear leucocytes, and subendothelial as well as mesangial deposits. The deposits sometimes appear as crystals, but more often have a fibrillar character, thought to be typical of cryoglobulins (32,33). Moreover, usually there is a close correlation between composition of the isolated cryoglobulin and glomerular deposits (29). The pathogenesis of glomerulonephritis in these cryoglobulinemias, in contrast to bland glomerular changes seen in most dysproteinemias, is not clear. Several possibilities have been offered: (1) Physicochemical features of the cryoprotein in the circulation may cause spontaneous aggregation, activation of complement proteins, and deposition of phlogogenic complexes in the kidney; (2) the monoclonal protein may have antiimmunoglobulin activity, form immune complexes in the circulation and deposit like other immune complexes in the kidney; (3) the monoclonal protein may have autoantibody characteristics with binding to tissue sites (3,34), or to other circulating antigens, such that immune complexes result and deposit. Although it is reasonable to assume that the circulating monoclonal cryoglobulin induces the glomerulonephritis, formal proof of this hypothesis in clinical immunopathology has only been done once (35).

B. Renal disease as a contributory cause of cancer.

In the foregoing discussion the kidney has been injured anatomically or

functionally in the course of ongoing neoplasia. There also appear to be actual or potential threats among patients with renal insufficiency for the development of a variety of cancers. The propensity for development of new tumors in patients who have received renal transplantation and, perforce, been treated with immunosuppressant medications, and tumors complicating cytotoxic therapy of patients with chronic disease (36) are not at issue here and will not be discussed. Rather, I will concentrate on several different situations that appear to present a special hazard for development of new malignancies.

1. Analgesic use: The hazards of analgesic use, particularly phenacetin containing compounds, have come to widespread clinical recognition relatively recently. The important epidemiologic study reported by Murray and Goldberg (37) clearly established analgesic-associated nephropathy as a major clinical problem and an important cause of otherwise unexplained renal failure in this country. In many communities, particularly in Europe and Australia it is considered even more common cause of renal failure than in the United States. However, despite this acknowledged association, reports of transitional cell (urothelial) carcinomas of urinary tract occurring in this same group of patients have not received much attention. Transitional cell carcinomas of the urinary tract usually occur in the urinary bladder, and tend to occur in older males. Hultengren and co-workers (38) in Sweden first reported several patients with renal pelvic epithelial tumors who also had renal papillary necrosis, a pathologic and clinical hallmark of "analgesic abuse". In a prospectively identified group of 104 patients with strong histories for phenacetin, antipyrine, and caffeine-containing proprietary drugs who had clinical nephropathy, 11 were observed to develop urothelial carcinomas, 9 of the upper urinary tract (39). Since then, several reports have emphasized the relationship of analgesic-associated nephropathy and transitional cell carcinomas of the kidney and ureter. A recent report from North Carolina by Gonwa and associates (40) is particularly instructive, as they (1) reviewed all cases of transitional cell carcinoma to identify features also marking analgesic nephropathy and (2) prospectively observed development of such tumors in patients already identified as having probable analgesic-associated nephropathy. Table IV highlights some of the important features of the first group.

Table IV CHARACTERISTICS OF PATIENTS WITH TRANSITIONAL CELL CARCINOMA FROM REVIEW OF GONWA AND ASSOCIATES

	patients with analgesic nephropathy	patients without analgesic nephropathy
total	6	109
male	2	79
female	4	30
bladder tumor (%)	3 (50)	107 (98)
renal pelvis tumor (%)	3 (50)	2 (2)
died	3	12

Several noteworthy points have been made by Bengtsson and associates (39):

(1) recognition of these upper tract tumors comes later than clinical renal disease, is usually associated with micro- or gross hematuria, and "manifest development of the tumor often came after cessation of drug abuse". (2) Thirty-five percent of the patients have had a second urothelial tumor, and bilateral disease has occurred frequently. (3) The outcome in terms of long term prognosis has not been good, with high mortality apparently due to extensive tumor.

The pathogenesis of these neoplasms is not proven, but the obvious association with long-term drug usage has suggested that phenacetin metabolites or other components of the drug mixtures, or combinations of them are carcinogenic. Phenacetin in experimental animals is capable of inducing dysplastic changes in the renal papilla. Bengtsson particularly has suggested an "induction time" for carcinogenic effect, pointing out a similarity to carcinogenic induction of urothelial tumors by chemical dyes and Thorotrast urographic studies.

2. Acquired cystic disease of the kidneys in hemodialysis patients: a new syndrome: Dunnill and co-workers (41) made the first systematic report of cystic transformation of kidneys in hemodialysis patients. During an 8 year period 236 patients were accepted in their unit for long-term intermittent hemodialysis; 51 patients died, and 30 were autopsied. Among these 30, they reported a multicystic transformation of otherwise small kidneys in 14 patients who had dialyzed for 4 months to 7 years. This transformation was widespread, and in some kidneys virtually replaced the parenchyma; moreover, it was accompanied in 8 of the 14 by single or multiple renal tumors: papillary, tubular or solid. One of the 14 patients died of metastatic renal cell carcinoma. In addition, some of these patients clinically had hematuria, perirenal or intracystic hemorrhage.

In the last 2 years there have been several publications, all of which suggest that 20-50% of autopsied dialysis patients have a frequency of cystic transformation of their native kidneys. In all these reports papillary intracystic growths (papillary cystodenomas) and solid tumors (adenomas) have been found in a higher frequency than they are reported in usual autopsy series, at a younger age, and in the company of the cystic changes. Moreover, the cystic changes are more widespread, and have a different microscopic character than simple cysts of the kidney, and have not been found in "control" populations of cases with known undialyzed renal disease. In the series reported by Hughson and associates (42) the material examined comprised mainly nephrectomized organs from patients anticipating renal transplantations.

The pathogenesis of this cystic transformation is not clear, and suggestions include obstructed tubules, toxic effects of metabolites or crystals retained or concentrated in the kidney, and ischemia due to the marked muco-fibroblastic intimal proliferation of arteries and arterioles characteristic of the dialysis kidney. Moreover, the relationship of these cysts to the tumors is not clear. There is no question that there is a unique statistical association between the cysts and the renal tumors, and the occurrence of both in a age population characteristic for neither (42,43). There is, apparently, controversy in general as to whether cystic change should be considered a precursor to renal cell tumors, quite independent of the present concern raised regarding dialysis patients. Further, there is a rather arbitrary distinction made by many between renal adenoma and renal cell carcinoma: this is based on size. A renal adenoma less than 2-3 centimeters may be considered benign, whereas one larger than 2-3 centimeters is called renal cell carcinoma. This is because these tumors often are

characterized histologically by low grade atypia, uncertain biologic activity, slow growth, and usual occurrence at a late age.

Two recent reports are noteworthy, however. Ishikawa and associates (44) studied 96 patients who had been on chronic hemodialysis, using computer-assisted tomography and a quantitative volumetric measure of kidney size. They concluded that kidney volume decreased during the first 3 years of chronic dialysis, but increased in many after 4 years. They found multiple cysts in 43.5% of patients on dialysis less than 3 years, in 79.3% of those dialyzing longer than 3 years, and in 100% of those dialyzing more than 3 years who had kidney volume exceeding 50 ml. Konishi and co-workers (43) reported on 4 of the 96 patients studied who were nephrectomized: all had acquired cystic disease, cystadenomas, and adenomas, moreover, 3 had renal cell carcinoma. These patients ranged from 24 to 28 years of age, and each had been dialyzing for 6-8 years.

3. De Novo malignancy in chronic hemodialysis patients: Three clinical circumstances seem accompanied by greater risk of clinical neoplasia, particularly lymphoproliferative disorders and acute myelocytic leukemia: congenital immunodeficiency syndromes, cytotoxic chemotherapy of cancer, and renal transplantation. In general, this susceptibility has been attributed to a common deficiency of immunological surveillance, either natural or chemically induced (immunosuppression). This concept has derived from the clearer definition of cellular and humoral immunity, their regulatory and integrating mechanisms, and the clonal selection hypothesis. Simply stated, the concept of immunological surveillance implies that ongoing cellular immune mechanisms are responsible for recognition and suppression or elimination of mutant or neoplastic clones of cells. As discussed by Louie and Schwartz (45) these aforementioned clinical situations are characterized by defective DNA and genetic material, high rates of tissue turnover and consequent risks of cumulative genetic mutations, and/or chronic antigenic stimulation, with or without superinfection by oncogenic viruses. They argue to distinguish defective surveillance from underlying potent oncogenic stimuli which may overpower intact cellular immune mechanisms.

On the other hand, there has been great interest regarding integrity or compromise of immunological mechanisms in the uremic patient. Original concerns were directed to the susceptibility to infection of the patient with renal insufficiency (46). However, as renal transplantation focused new attention on patients with renal failure it became clear that their cellular immunity may be clinically compromised in at least 3 ways: (1) deficiency of expression of skin tests, (2) prolongation of skin graft survival, and (3) prolongation of renal allograft survival (47,48). These clear, undisputed, and unequivocal characteristics have been tested extensively in recent years by a variety of *in vivo* and *in vitro* challenges. However, the evolution of medical practice during recent years has added an enormous complicating dimension to the paradigm: no longer are patients "uremic" in the sense of unrestrained chemical and metabolic derangements, but they are much healthier and more stable, albeit using some dialytic device(s).

This is the question that has been raised and remains unresolved: Is chronic renal insufficiency associated with a greater than normal risk of malignancy? Several papers have appeared since Matas' (49) which purported to document at least a seven-fold greater incidence of cancers among patients

with serum creatinine concentrations exceeding 2.5 mg/dl, and progressing to dialysis and/or renal transplantation. In the main, virtually all of these reports show statistically that hemodialysis patients are at greater than normal risk to express some visceral cancer (50,51). Moreover, the tabulation of cancers diagnosed clinically and pathologically describes principally epithelial and solid organ cancers with more usual frequency patterns in an adult population, compared to patients with congenital immunodeficiency syndromes, subjects treated with cytotoxic therapy, or renal (and cardiac) transplant recipients. This feature is more in accord with Schwartz's formulation of deficient immunosurveillance.

Tables V, VI, and VII tabulate data from our own records at the Dallas Veterans Medical Center in three major categories: (a) patients with documented visceral neoplasm(s) antecedent to development of renal insufficiency, (b) patients presenting with neoplasm and renal insufficiency concomitantly, and (c) patients who have developed recognizable neoplasms while on hemodialysis. I exclude skin cancers. No patient had received cytotoxic or immunosuppressant therapy. Moreover, all patients are men. You will be struck, as I am, that several patients who started with tumors have gone the course of their tumors: where adequately treated, they are alive, and compensated renal insufficiency on hemodialysis has not been complicated by recurrence so far. On the other hand, 6 patients of the 237 we have managed on hemodialysis have developed visceral cancers, and most of these have died as a complication thereof. In each of these patients the tumor has been a common one, compatible with the age, sex, and (bad) habits of the patients we manage. At the present time I do not have an answer to the critical question regarding the real risk for hemodialysis patients to develop neoplasia, primarily because I am unconvinced that I have a definable data base or denominator to use in the calculations.

Table V PATIENTS MANAGED BY CHRONIC, INTERMITTENT HEMODIALYSIS AT DALLAS VAMC WHO HAD HISTORY OF MALIGNANCY DIAGNOSED AND TREATED BEFORE ONSET OF END-STAGE RENAL DISEASE OR HEMODIALYSIS

Patient	Age at start of dialysis	years dialyzed	tumor type	dead	death from malignancy
1	59	1	renal cell carcinoma	+	+
2	63	1.5	multiple myeloma	+	+
3	63	3	retic cell sarcoma		
4	64	3	bladder	+	
5	55	.7	multiple myeloma	+	+
6	64	1	multiple myeloma		
7	62	4	renal cell carcinoma		
8	68	3	renal cell carcinoma		
9	58	4	renal cell carcinoma		

Table VI PATIENTS HEMODIALYZED AT DALLAS VAMC WHO HAD CONCOMITANT ONSET OF MALIGNANCY, AND END-STAGE RENAL DISEASE REQUIRING HEMODIALYSIS

Patient	age at start dialysis	tumor type	duration of survival after dialysis started	dead	death from malignancy
10	48	hepatoma	6 months	+	+
11	66	renal cell carcinoma	1 year		
12	53	colon carcinoma	5 years		
13	72	melanoma of colon	1.5 years	+	+

Table VII PATIENTS WHO APPARENTLY DEVELOPED MALIGNANCY de novo WHILE RECEIVING CHRONIC INTERMITTENT HEMODIALYSIS UNDER DVAMC AUSPICES

patient	age at start dialysis	years dialyzing	tumor type	dead	death from malignancy
14	54	1.3	hepatoma	+	+
15	53	5	lung	+	+
16	64	8	lung	+	+
17	54	5	lung	+	+
18	64	8	pancreas	+	+
19	56	2	hepatoma	+	+

In this regard, also, I should mention that there is so far only one negative paper on this subject (52), wherein age-risks were incorporated, and that paper concluded only that female dialysis patients had a far greater than expected risk of two tumors: lymphosarcoma and cancer of the kidney.

Conclusion

The immune system is involved on one hand in the causal development of renal insufficiency complicating neoplasms in two principal ways: (a) an autoimmune mechanism, or (b) exporting a product of functioning lymphoid cells which is toxic to the kidney. In the former circumstance, the tumor may elicit antitumor antibodies, or in some way provoke a more general autoimmune nephritogenic mechanism. In the latter, the product(s) of these cells may cause nil lesion nephrotic syndrome or some direct tissue-deposit nephropathy (amyloid, light chains, casts, or crystals). On the other hand, the breakdown of immunological integrity implied in effective immunological surveillance is more difficult to define in renal insufficiency - more specifically, in hemodialysis patients. In the three specific circumstances examined, different variables appear to operate: (a) analgesic abuse appears to induce clinically apparent tubulointerstitial disease before transitional cell carcinomas become apparent.

This may occur because renal damage is dose-dependent, whereas carcinogenic induction follows a different pathway and is time-dependent expression of the risk. (b) Cystic transformation of the kidneys and development of dysplasias and new neoplasms appears to occur in kidneys that are no longer functionally important to the organism - either when the patient has progressed to dialysis therapy or received a renal graft. Again, this is a time-dependent evolution, which may be accentuated and accelerated by retention, metabolism, and storage of metabolites (e.g., oxalate crystals) in high concentration, in an ischemic environment, relatively sequestered from immunological traffic and "surveillance". (c) the problems of neoplasia in a dialysis population comprise a totally new and unique risk of uncertain importance. It is a consideration only because an evergrowing "new" population confronts us, with a totally different milieu and metabolic set of counter-regulatory systems. The contribution to this environment of the many new variables - plastics, plasticizers, trace chemicals, vitamin deficiencies, etc., - are not defined yet.

In summary, kidney disease may be the first clue to a visceral neoplasm, and patients with new onset renal disease should be considered from that perspective. Alternatively, patients with established renal disease, renal insufficiency, and particularly, dialysis patients, should be considered potentially at risk for later development of visceral neoplasms. If all these things be true, then the greatest potential impact may be made by preventive medicine - elimination of nephrotoxic and carcinogenic variables, periodic, invasive diagnostics, and - hopefully - early detection of incipient neoplasms.

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