Renal Cell Carcinoma in Patients With a Personal or Family History of Hematologic Malignancies

Janice P. Dutcher, MD, and Peter H. Wiernik, MD

The authors are affiliated with the Cancer Research Foundation of New York in Chappaqua, New York. Dr Dutcher is an associate director and Dr Wiernik is the director.

Corresponding author:
Janice P. Dutcher, MD
750 Kappock Street, # 511
Bronx, NY 10463
E-mail: jpd4401@aol.com
Tel: 914-316-7809

Abstract: A little-appreciated association between renal cell carcinoma (RCC) and hematologic malignancies (HMs) has been reported for at least 20 years. The HM characteristically occurs first in patients with both neoplasms, and the large majority (94%) of these HMs are of B-cell origin. Furthermore, the majority of patients with RCC and an HM are male. Recently, we have noted an increased incidence of HMs in families of patients with RCC and are exploring this observation further. Here, we summarize our reports on the association between these neoplasms in individual patients and review the relevant literature.

Keywords
Familial malignancies, hematologic malignancies, renal cell carcinoma

Introduction

Patients with non-Hodgkin lymphoma (NHL) or other B-cell malignancies have an increased incidence of other primary malignancies, including solid tumors.[1,2] For example, an increased incidence of solid tumors in patients with chronic lymphocytic leukemia (CLL) has been well documented.[3] Two large epidemiological studies based on the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database identified an association between renal cell carcinoma (RCC) and NHL, and demonstrated an observed to expected ratio of 1.47 when RCC followed NHL among a database[1] of 29,153 patients collected from 1973 to 1987. A subsequent evaluation of another 6171 patients diagnosed with NHL as the initial primary tumor, from 1965 to 1980, found an increased risk of subsequent RCC in those patients.[2]

We and others have reported an increased co-incidence of RCC and hematologic malignancies (HMs), the majority of them B-cell disorders.[4-16] Since our initial report,[7] we have continued to collect information on and report additional cases of this association.[8] This article contains an updated review of the literature, providing data on 189 patients to date with both RCC and an HM (Table 1).[4-48] Clearly, this is not as unusual a phenomenon as previously thought. From our previous reports, and from reports in the literature, several features of this association appear to be characteristic. We comment on these features below.

Table 1. Patients With Both RCC and an HM

No. of Patients	Male:Female	RCC First	HM First	Synchronous
189	126:56 (2.25:1)[a]	41 (22%)[b]	82 (43%)	62 (33%)

HM, hematologic malignancy; RCC, renal cell carcinoma.

[a] Information not available for 7 patients.

[b] Information not available for 4 patients.

Data from references 4 through 48.

Features of Patients With RCC and Hematologic Malignancies

In 2006, we reported on 9 patients with a personal history of RCC and HM, and noted the following characteristics: (1) there was a male predominance, with 8 males and 1 female; (2) the HMs were all of B-cell origin, with 4 being extranodal and 2 of the patients having Hodgkin lymphoma (HL); and (3) the HMs developed first in 5 of the 9 patients, and the diseases were concurrent in 2 patients. In our review of the literature in that report, we confirmed those characteristics to be consistent with the other reported series and cases.[7]

In a subsequent update of our patient series (16 total patients), those characteristics remained evident.[8] Of those 16 patients, 11 were male and 5 female, with a median age at RCC diagnosis of 63 years (range, 36-82 years).[8] These are the same demographics as our initial report. All 16 patients had HMs of B-cell origin, including five with large B-cell lymphoma, two with small cell lymphoma, four with HL, two with CLL, two with monoclonal gammopathy of uncertain significance (MGUS), and one with hairy cell leukemia. Five lymphomas were extranodal.[8] In our series, the predominant RCC diagnosis was clear cell histology (11 patients), with 2 papillary and 1 each of oncocytoma, poorly differentiated, and renal cancer not otherwise specified. Among these 16 patients, the most common sequence of diagnosis was an HM followed by RCC (10/16 patients; 63%), which is consistent with our initial report and with that of other patients in the literature.[7]

We have collected data on an additional 64 patients from the literature since our first summary of 125 reported cases. We examine the features of these cases in Table 1, which includes our series. Table 1 comprises 189 patients with both RCC and a hematologic malignancy. Of these, 126 patients are male and 56 are female (the gender of 7 patients is not specified), for a male:female ratio of 2.25:1. For the 134 patients with lymphoma in whom gender is known, the male:female ratio is 2.2:1. Although this is expected in RCC (population studies and literature both show a male:female ratio of 2:1 for patients with RCC), it is not the case for NHL or other lymphoid malignancies. The reported male:female ratio for NHL is 1.2:1. In our prior review of the published series of RCC and HMs,[7] the male:female ratio for NHL was 2.2:1. In our current expanded series, the male:female ratio is 6:1 among those with NHL and 2:1 among all those with B-cell malignancies. Therefore, the expanded literature review continues to demonstrate the same male predominance among patients with HMs in the setting of RCC that we observed in our initial report.

Table 2. Summary of Diagnoses of HMs in Patients With RCC and an HM

Malignancy	No. of Patients
Lymphoma[a]	136
Other lymphoid diseases	42
MM	16
CLL	12
HL	5
MGUS	3
WM	2
ALL[b]	2
Plasmacytoma	1
HCL	1
Myeloid leukemias	11
CML	6
APL	3
AML	2
Total patients[c]	189

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HCL, hairy cell leukemia; HL, Hodgkin lymphoma; HMs, hematologic malignancies; MGUS, monoclonal gammopathy of uncertain significance; MM, multiple myeloma; WM, Waldenström macroglobulinemia.

[a] Including 2 T-cell

[b] Including 1 T-cell

[c] Total lymphoid HMs, 178; total B-cell HMs, 175

Whereas in our initial series we reported only 1 patient with a synchronous diagnosis, the literature reports synchrony more frequently. Among the patients listed in Table 1, a total of 82 developed the HM first (43%), and 62 were diagnosed with RCC and an HM simultaneously (33%). Of the 189 patients with RCC and an HM, 175 were diagnosed with a B-cell HM and 3 were diagnosed with a T-cell HM, for a total of 178 lymphoid malignancies among the 189 patients (94%) with RCC and an HM (Table 2).

Among the RCC patients listed in Tables 1 and 2, a total of 136 patients developed lymphoma. Sixteen patients had multiple myeloma (MM; 2 patients initially presented with plasmacytoma that rapidly evolved

into full-blown MM) and 12 patients had CLL, all of B-cell origin. Additional B-cell malignancies were HL (5 patients), MGUS (3 patients), Waldenström macroglobulinemia (2 patients) and 1 patient each with hairy cell leukemia, plasmacytoma, and B-cell acute lymphocytic leukemia (ALL). There was also 1 patient with T-cell ALL (Table 2).

The concordance of HL and RCC is rare in the literature; there was only 1 reported case in the multiple series reviewed in our prior report.[4-6,9-16] We have since reported on 4 patients with HL who subsequently developed RCC in our updated series,[8] but have not found additional reports in the literature since our previous review.

In our initial report of RCC and an HM in the same patient, we described four of 9 lymphomas in extranodal sites, not including patients with CLL, hairy cell leukemia, and MGUS,[7] and Ohsawa and colleagues also described such cases.[4] Epidemiologic studies of lymphoma show a global variation in overall incidence of lymphoma, but the percentage of those with extranodal presentation appears to range between 25% and 35% in each setting.[49-51] We have tabulated the cases with extranodal sites of lymphoma in Table 1, and found that among the 136 patients with lymphoma and RCC, there were 43 with extranodal lymphoma (32%). This frequency is within the range reported for lymphoma patients in general, as noted above (Table 3).[49-51]

A new development noted in several recent reports (within the past 10 years or less) is the diagnosis of myeloid leukemias in patients with RCC. The literature includes 6 cases of chronic myeloid leukemia (CML), two of acute myeloid leukemia (AML), and three of acute promyelocytic leukemia (APL; Table 2).[41-48] Of those 11 patients, 5 adults were discovered to have renal tumors concurrently with the initial diagnosis and management of their leukemia (2 CML, 2 APL, 1 AML).[43-45,47] One child with APL in complete molecular remission developed pediatric RCC 5 years later.[48] The same sequence and pattern of diagnosis was observed in the 2 children with ALL who, as adolescents in remission from ALL, developed pediatric RCCs.[29,40] Two adults had undergone nephrectomy as their only treatment for RCC, and subsequently developed leukemias 2 and 3 years later.[42,46] Three additional patients developed CML after multiple years of antivascular endothelial growth factor tyrosine kinase inhibitor (TKI) therapy for metastatic RCC.[41] All the authors have raised concerns of therapy-induced secondary malignancies, but it is difficult to develop a consistent theory when 5 cases are synchronous, 2 patients with RCC had no systemic therapy prior to leukemia, and the 3 children had different treatments for their leukemias prior to their RCCs. A review of 1445 patients with a CML/myeloproliferative neoplasm diagnosis compared the incidence of second malignancies following treatment with antileukemic TKIs vs the SEER database, and found a lower than expected incidence of second malignancies, with the incidence of secondary renal cancer being 4%.[52] It is possible that we are more commonly observing an association of myeloid leukemia and RCC as a consequence of improved survivorship for CML, APL, AML, and now RCC, potentially allowing time for the development of the second malignancy to appear, perhaps as a delayed manifestation of the initial disease. It should be remembered that central nervous system leukemia as a manifestation of childhood ALL was rarely seen until effective therapy was developed for the common initial presentations of the disease, and that renal disease in diabetics was essentially unheard of until insulin was available. Obviously, a search for common molecular pathways will continue.

Table 3. Patients With Extranodal Lymphoma and RCC

Reference	Extranodal Patients	Site of Lymphoma
4	18	3 central nervous system; 2 Waldeyer ring; 2 oral cavity; 7 gastrointestinal tract; 4 other
5	2	2 MALT lymphoma of stomach
8	5	1 each: subcutaneous tissue; perirenal mass; nasal; lung; small bowel
9	1	Parotid mass
10	5	2 kidney; 1 MALT lymphoma of stomach; 2 bone marrow
11	1	Kidney
12	1	Cutaneous
13	1	Bilateral testes
14	1	Subcutaneous tissue of breast + intravascular lymphomatosis
15	1	MALT lymphoma of right orbit
17	1	Paranasal sinus
27	1	Sacral mass
32	1	Lung + liver + bone + nodes
33	1	Kidney + liver + pancreas + gastrointestinal tract
34	1	Ipsilateral adrenal gland
36	1	Bone marrow
37	1	Kidney
Total	43[a] (32%)	

MALT, mucosa-associated lymphoid tissue.

[a]Total lymphomas, 136.

Families With RCC and HMs

The observation of families having multiple members with HMs is well documented, and includes families with a predominance of one type of HM, and families with multiple types of HMs. Wiernik and colleagues have developed a familial registry containing more than 750 pedigrees of families with multiple hematologic malignancies, and have reported on many of these.[53] The phenomenon of anticipation has been demonstrated in most families, suggesting a possible genetic component.[53]

Of note, among these families are members with a variety of adenocarcinomas, and Wiernik and Etkind have explored the association of breast cancer and lymphoma in the same patient.[54-56] In view of these observations, and the occurrence of RCC and an HM in the same patient, we have begun to explore the association of HM in families of patients with RCC. We have prospectively and retrospectively reviewed family histories among more than 700 patients with RCC. We have presented preliminary data and are continuing our investigations.[57-59] As of our report in 2013, a family history of HM was observed in 74 relatives, involving 59 families of patients with RCC. Similar to our data concerning the occurrence of RCC and an HM in the same patient, the most common HMs in family members were B-cell disorders (NHL, MM, CLL, Waldenström macroglobulinemia, and HL). There were also several with myeloid disorders, but these accounted for less than 10% of the cases. The demographics of the RCC patients were similar to the general RCC literature. The relatives were primarily first- and second-degree relatives, with only a handful being more distant. This is an ongoing project and will be the subject of further publications.

Summary and Potential Explanations for RCC/HM in the Same Patient

A number of hypotheses have been proposed for this increasingly reported phenomenon of RCC and an HM occurring in the same patient. The majority of these cases have been lymphoid hematologic malignancies, suggesting a possible immunologic explanation. Anderson and colleagues have proposed immune dysregulation during a response to the adenocarcinoma leading to lymphoid proliferation and then lymphoid malignancy.[5] This hypothesis might explain those cases in which there is synchronous development of both malignancies, some with collision histology, and for those in which lymphoma follows RCC. However, there is a large group (43%) in which the HM occurs first, thus requiring another explanation.

Another hypothesis that has been demonstrated in some concurrent malignancies is an infectious agent that either causes or facilitates both diseases. An example is mucosa-associated lymphoid tissue (MALT) gastric lymphoma and gastric adenocarcinoma, both caused by *Helicobacter pylori*.[60] Wiernik and colleagues have noted an increased association of breast cancer and NHL in the same patient, in which the breast cancer was usually the first malignancy. Although the breast cancer in those patients was not treated with systemic therapy, NHL—mostly low-grade B-cell NHL—followed years later.[54] Etkind and Wiernik reported mouse mammary tumor virus (MMTV)–like *ENV* gene sequences in both malignancies of many of these patients.[55,56] MMTV can cause breast cancer in female mice and lymphoma in male mice.

A genetic basis for the association is also a prime consideration. Both NHL and RCC have several common chromosomal abnormalities, including deletion of 17p and mutation of 3p.[61-63] However, these are large regions of chromosomes, and it is yet to be determined if the identical genes are changed or lost in the RCC and the lymphoma. Deletions or methylations of the gene for von Hippel–Lindau syndrome (the *VHL* gene) are common in RCC, but a role in lymphoma or other B-cell malignancies is yet to be demonstrated.

With regard to the association with plasma cell disorders, the role of interleukin-6 is often mentioned, as it is a growth factor for plasma cells and in some cases for RCC, and can be produced by RCC.[30] Whether this plays a legitimate role in progression of either disease is yet to be determined.

More recently, in the era of molecular genomics, a number of new associations are being discussed as potential mutual pathways. *PTEN* germline mutations have been recognized in multiple familial cancer syndromes, including a recent report of hereditary kidney cancer.[64,65] Loss of *PTEN* can activate mammalian target of rapamycin (mTOR), which is central to RCC growth. Inhibition of mTOR has become one of the new therapeutic strategies for RCC.[66,67] Recently, studies have suggested a role for *PTEN* deletion in a variety of lymphomas and lymphoid leukemias, both B-cell and T-cell, and this rather central pathway could be a major component of the association of RCC and lymphoma, and possibly other hematologic malignancies.[68-71]

In addition, certain key genes are being identified as important in hereditary RCC, and these are ideal targets to evaluate in patients with both RCC and an HM and in families with both diseases.[72-75] Furthermore, several other tumor suppressor genes have been identified near the *VHL* gene, and some of these play a role in specific types of RCC and in hereditary RCC syndromes.[75-77] Again, these should be considered for investigation in patients with RCC and an HM and families with both neoplasms. Others have speculated that microRNA dysregulation of transcription can promote development of

several malignant phenotypes arising from similar altered molecular pathways (oral communication, C. M. Croce, MD, December 2014).

Another recently presented hypothesis is a potential role of aging and the development of RCC, via a connection between *VHL* and progerin.[78] Because RCC is associated with older age, this concept is of interest, but it does not yet explain the connection to HM directly.

Finally, Guo and colleagues reported a patient with synchronous RCC and mantle cell lymphoma who also had a gastrointestinal stromal tumor.[38] This patient's tumors were evaluated by comparative genomic hybridization, and all of these tumors had an increase in nuclear staining of nuclear factor κB, suggesting activation of this pathway. The patient was also evaluated for activation of proinflammatory cytokines in the serum, many of which were elevated but some of which were not, such that a pattern could not be fully defined. The authors speculated that activation of common pathways may lead to divergent malignancies. They could not determine whether the alterations developed independently in the different tissues or through a common inciting source. These findings, however, suggest that mutual activation of aberrant pathways can lead to multiple tumors.

Summary

A little-appreciated association between RCC and B-cell HMs has been reported for at least 20 years. Myeloid malignancies may be involved as well, whether treatment-related or due to enhanced survivorship with newer treatments, giving new diseases time to arise. Better molecular characterization of all of these diseases may lead to identification of common pathways that facilitate malignant transformation. The clinical observations of these associations, which are more frequent than predicted, should provide impetus for further exploration of genetic mechanisms of neoplasia.

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Disclosures

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