Associated Malignancies in Patients with Waldenström's Macroglobulinemia and Their Kin

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Abstract

We examined the incidence of other malignancies in 924 Waldenström's Macroglobulinemia (WM) patients and their kin. A total of 225 (24.3%) patients had ≥ 1 additional malignancy, with 63% predating the WM diagnosis. The most common gender-adjusted malignancies were prostate (9.4%), breast (8.0%), non-melanoma skin (7.1%), hematologic (2.8%), melanoma (2.2%), lung (1.4%) and thyroid 1.1%). Among hematologic malignancies, all 13 cases of diffuse large B-cell lymphoma and 4 cases of acute myelogenous leukemia were diagnosed after WM, and were therapy-related. Familial WM subgroup analysis showed a higher incidence of prostate cancer (P = .046) in sporadic WM patients, while patients with familial WM had a higher incidence of lung cancer (P = .0043). An increased incidence of myeloid leukemias (P < .0001) was reported among kin of familial WM patients. These data reveal specific cancer associations with WM, and provide a basis for exploratory studies aimed at delineating a common genetic basis. Additionally, these studies suggest specific cancer clustering based on familial predisposition to WM.

Introduction

Waldenström's macroglobulinemia (WM) is a B-cell lymphoproliferative disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells, along with demonstration of an IgM monoclonal gammopathy.[1] The diagnosis of monoclonal gammopathy of undetermined significance (MGUS), particularly IgM MGUS, is associated with an increased risk of developing WM [2]. Although the etiology of MGUS and WM is unknown, there is evidence to support a role for genetic factors and familial predisposition.[3-7] Familial predisposition is common in WM as up to 20% of WM patients have a first degree relative with either WM or a closely related B-cell disorder.[6] Three possible subtypes for WM predisposition have been proposed.[8-10] These include: (1) sporadic, proband has WM, but there is an absence of WM or other B-cell disorders in other family members; (2) familial, mixed B-cell disorders subtype; proband has WM, and various B-cell disorders are manifested by other family members; and (3) familial, multiple WM cases subtype; proband has WM, and at least one other family member has WM.

While the above studies suggest a separate genetic predisposition for WM, evaluating the risk of other cancers among all WM patients and their kin, may herald important information for common genetic risks to cancer. We therefore evaluated the incidence of other cancers in patients with WM, and their first degree relatives, as self-reported by patients.

Patients and Methods

We examined the records of 924 consecutive WM patients seen at the Bing Center for Waldenström's macroglobulinemia at the Dana Farber Cancer Institute since 1999. All self-reported cancers, including those that occurred before and after the diagnosis of WM were evaluated. Further data collected included gender, self-reported ethnicity, age at diagnosis of WM, timing of diagnosis of other cancer(s) relative to WM diagnosis, WM treatment(s), and family cancer history. Patients were classified by familial WM subtype for analysis. The study was approved by the Dana Farber Cancer Institute/Harvard Cancer Center Institutional Review Board.

Statistical Analysis

Comparison of pre- and post-treatment parameters was performed using a 2-tailed students t test on Microsoft Excel™ software. For non-parametric testing of pre- and post-treatment responses, Chi Square test (VassarStats) was used. A P value ≤ .05 was deemed to be significant for the above studies.

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Table 1 Non-WM Cancer Events in 924 WM Patients Subclassified by WM Familial Disease Presentation

Characteristic	Total	Sporadic	Familial, Mixed B-Cell	Familial, WM Only
Number of Patients	924	685	194	45
Median Age at WM Diagnosis	59 (range 29-91 years)	60 (range 29-91 years)	58 (range 36-85 years)	61 (range 35-89 years)
Male/Female	573/351	439/241	109/90	25/20
Prostate (Males)	54 (9.42%)	47 (10.7%)	5 (4.59%)	2 (8.00%)
Breast (Females)	28 (8.00%)	22 (9.13%)	6 (6.67%)	0 (0.00%)
Skin (Non-Melanoma)	66 (7.14%)	56 (8.18%)	10 (5.15%)	0 (0.00%)
Hematologic	26 (2.81%)	16 (2.33%)	8 (4.12%)	2 (4.44%)
Melanoma	20 (2.16%)	15 (2.19%)	4 (2.06%)	1 (2.22%)
Lung	14 (1.40%)	5 (0.73%)	8 (4.12%)	1 (2.22%)
Thyroid	10 (1.08%)	10 (1.46%)	0 (0.00%)	0 (0.00%)
GYN	10 (1.08%)	8 (1.16%)	2 (1.03%)	0 (0.00%)
Colon	7 (0.75%)	6 (0.88%)	0 (0.00%)	1 (2.22%)
Bladder	9 (0.97%)	8 (1.17%)	1 (0.52%)	0 (0.00%)
Renal	8 (0.86%)	7 (1.02%)	1 (0.52%)	0 (0.00%)
Other	21 (2.27%)	15 (2.19%)	5 (2.56%)	1 (2.22%)
Total	273 (29.6%)	212 (31.4%)	53 (25.8%)	8 (17.77%)

Table 2 Non-WM Cancer Events in 924 WM Patients, Classified by Occurrence Pre- or Post-WM Diagnosis

Characteristic	Total Events	Pre-WM (% of All Events)	Post-WM (% of All Events)
Prostate (Males)[a]	54 (9.42%)	685	23 (42.6%)
Breast (Females)[a]	28 (8.00%)	60 (range 29-91 years)	9 (32.1%)
Skin (Non-Melanoma)	66 (7.14%)	439/241	12 (18.2%)
Hematologic (All)	26 (2.81%)	47 (10.7%)	20 (76.9%)
Myeloid Leukemia	4 (0.44%)	22 (9.13%)	4 (100%)
B-cell malignancies	18 (1.94%)	56 (8.18%)	13 (72.2%)
T-cell malignancies	3 (0.33%)	16 (2.33%)	2 (66.7%)
Other	1 (0.11%)	15 (2.19%)	1 (100%)
Melanoma	20 (2.16%)	5 (0.73%)	5 (25.0%)
Lung	14 (1.40%)	10 (1.46%)	10 (71.4%)
Thyroid	10 (1.08%)	8 (1.16%)	2 (20.0%)
GYN	10 (1.08%)	6 (0.88%)	1 (10.0%)
Colon	7 (0.75%)	8 (1.17%)	4 (57.1%)
Bladder	9 (0.97%)	7 (1.02%)	6 (66.7%)
Renal	8 (0.86%)	15 (2.19%)	7 (87.5%)
Other	21 (2.27%)	212 (31.4%)	2 (9.5%)
Total	273 (29.6%)		101(36.9%)

[a]Adjusted for gender. GYN = includes any non-gynecologic breast cancers.

Results

Patient characteristics were as follows: of the 924 patients, 573 (62.0%) were male. The median age at diagnosis for these patients was 59 (range, 29-91 years). Eight-hundred sixty two (93.3%), 11 (1.19%), 8 (0.86%), 4 (0.43%), and 39 (4.22%) reported a Caucasian, African, Asian, Hispanic, unknown, or other including mixed racial heritage, respectively. Of 740 patients who reported their ethnic heritage, 143 (19.3%) were of Jewish decent, with most of these patients (n = 106; 74.1%) reporting an Ashkenazi (Eastern European Jewish) background. The familial presentation for WM disease for all 924 patients was as follows: sporadic (n = 685; 72.5%); familial, mixed B-cell disorders (n = 194; 22.6%); familial, WM only (n = 45; 4.9%). There was no difference in racial or ethnic distribution (data not shown), as well as age at diagnosis (Table 1) based on familial subtype. Of 924 patients, 225 (24.3%)

Table 3 Non-WM Cancer Events in First and Second Degree Kin of 924 WM Patients, Including Those Presenting With Sporadic and Familial WM

Event, n (%)	Events in Kin of all WM Patients	Events in Kin of Sporadic WM Patients	Events in Kin of Familial, Mixed B-Cell WM Patients	Events in Kin of Familial, Multiple WM Case Patients
Number of Patients	924	685	194	45
Patients with ≥ 1 Kin Solid Cancer Event(s)	579 (62.6)	430 (62.8)	121 (62.3)	28 (62.2)
Breast	206 (22.3)	159 (23.2)	39 (20.1)	8 (17.7)
Prostate	118 (12.8)	87 (13.0)	28 (13.4)	3 (6.66)
Lung	123 (13.3)	94 (13.7)	26 (13.4)	3 (6.66)
Colon	102 (11.0)	69 (10.1)	28 (14.4)	5 (11.1)
GYN	64 (6.9)	49 (7.2)	13 (6.7)	2 (4.4)
Gastric	41 (4.9)	27 (3.9)	11 (5.7)	3 (6.6)
Pancreatic	41 (4.9)	26 (3.8)	12 (6.2)	3 (6.6)
Hematologic				
Lymphoma	114 (12.3)	0 (0.0)	108 (55.6)	6 (13.3)
Lymph Leukemia	48 (5.2)	0 (0.0)	43 (22.1)	5 (11.1)
Myeloma	31 (3.4)	0 (0.0)	27 (13.9)	4 (8.9)
Myeloid Leukemia	43 (4.7)	18 (2.6)	21 (10.8)	4 (8.9)
Skin	26	19 (2.8)	6 (3.1)	1 (2.2)
Melanoma	26	20 (2.9)	5 (2.6)	1 (2.2)
Bladder	22	14 (2.0)	6 (3.1)	2 (1.0)
Thyroid	11	7 (1.0)	3 (1.5)	1 (2.2)
Renal	11	9 (1.3)	2 (1.0)	0 (0.0)

P = NS, for intergroup solid cancer comparisons. Comparisons omitted for B-cell malignancies since patients were stratified on basis of kin with B-cell malignancies. A higher incidence of myeloid leukemia events in kin of sporadic versus all familial WM patients combined ($P < .0001$); against familial mixed B-cell WM patients alone ($P < .0001$); or against familial, multiple WM case patients alone ($P = .05$) was observed.

reported at least 1 additional cancer to their WM. Among these patients, 181, 40, and 4 had 1, 2, and 3 additional malignancies to their WM, respectively, for a total of 273 non-WM cancer events.

For 167 patients (74.2%), the diagnosis of at least 1 malignancy predated the WM diagnosis. One hundred-seventy two non-WM cancer events occurred in these patients which are shown in Table 2. Eight-five patients with 101 non-WM cancer events occurred after the WM diagnosis. Sixty-seven of these 85 (79.2%) patients received treatment for WM. Comparison of non-WM cancer events which occurred prior to the WM diagnosis revealed a higher number of breast ($P = .036$), skin (non-melanoma; $P < .0001$), melanoma ($P = .0044$), and thyroid ($P = .0253$) cancers. In contrast, a higher number of lung ($P = .058$) and renal ($P = .012$) cancers were diagnosed post-WM diagnosis, and were related to co-incidental imaging for WM staging. Among hematologic malignancies, all 13 cases of diffuse large B-cell lymphoma and 4 cases of acute myelogenous leukemia were diagnosed after WM. These events occurred in treated patients and were deemed to be therapy-related.

By WM familial subtype, 212 (31.4%), 53 (25.8%), and 8 (17.8%) of non-WM cancer events occurred in sporadic; familial, mixed B-cell disorders; and familial, multiple WM cases patients, respectively (Table 1). A significant increase in non-WM cancer events was observed among sporadic versus familial patients (31.4% vs. 24.0%; $P = .03$). The breakdown for all non-WM cancer events for all 924 patients, as well as the distribution of these events by WM familial subtype is shown in Table 1. Comparison of non-WM cancer events among WM familial subgroups revealed an increased incidence of prostate cancer among WM patients with sporadic versus familial WM disease (10.7% vs. 4.6%; $P = .046$). Conversely, the incidence of lung cancer was higher among WM patients with familial versus sporadic disease (3.54% vs. 0.72%; $P = .0043$).

We next examined the incidence of cancers in kin, as self-reported by patients. First- and second-degree kin were considered for this analysis. The types of cancers reported in kin of WM patients are shown in Table 3. One thousand twenty-seven cancer events were reported among first- and second-degree kin of the 924 patients, including 791 nonhematologic cancers. Five hundred seventy-nine (62.6%) patients reported having at least 1 kin with a solid cancer. No difference in the percentage of patients reporting kin with a solid cancer, nor the distribution of solid cancer events among their kin was observed among WM patients when stratified by their familial WM presentation. A higher number of myeloid leukemia events was observed among kin of patients presenting with familial WM ($P < .0001$).

Discussion

We evaluated the risk of other cancers among all WM patients and their kin, in order to clarify if a common genetic risk may exist for WM with other cancers, and to clarify such risks in the context of familial WM predisposition. Similar to our efforts, Varettoni et al[11] recently observed an incrased risk of second cancers (1.66-fold)

among 220 consecutive WM patients in Italy, though most of these events occurred after the diagnosis of WM, and among patients who received treatment. The association of certain solid cancers including breast, genitourinary cancers, prostate, melanoma, and thyroid cancers with other B-cell malignancies has previously been reported,[12-19] though often are confounded by surveillance bias and treatment effect. The strength of this study is the relatively large population of patients studied for WM, as well as assessments of cancer events that occurred before and after the WM diagnosis and treatment. The most common gender-adjusted malignancies associated with WM which were observed in this study were prostate (9.4%), breast (8.0%), non-melanoma skin (7.1%), hematologic (2.8%), melanoma (2.2%), lung (1.4%), and thyroid (1.1%). In 17 male patients, a triad of WM with prostate cancer and either non-melanoma skin cancer (n = 11) or melanoma (n = 6) was observed. In the majority of these patients, the diagnosis of prostate cancer as well as non-melanoma skin cancers or melanoma predated the WM diagnosis. Among hematologic malignancies, all 13 cases of DLBCL and 4 cases of AML were diagnosed after WM, and were therapy related.

The association of WM with the cancers identified in this study may reflect a common genetic predisposition. Loss of 17p13.1 (p53) and 13q14 (retinoblastoma gene) by fluorescence in situ hybridization (FISH) is uncommon in WM,[20,21] and whole gene sequencing of p53 and BRCA1 and 2 genes by us in 6 WM patients did not demonstrate any mutations (unpublished observations). One other potential catalyst for the presentation of multiple cancers in WM patients may involve the loss of the glutathione-s-transferase enzymes GSTM1 and/or GSTT1 which catalyze the conjugation of glutathione (GSH). The loss of GSTM1 and GSTT1 has been reported in WM,[9] as well as in prostate, breast, lung, thyroid, and renal cancers.[22-24] It is noteworthy that more cancer events occurred in sporadic WM patients, versus those with familial WM history, and that certain cancers segway with familial history. In particular, twice as many prostate cases were seen among sporadic patients, whereas 5-fold more cases of lung cancer occurred in familial WM patients.

When cancer events were examined in context of timing of WM diagnosis, an increased number of cases of lung, renal, bladder, leukemia, and lymphoma cases occurred following the diagnosis of WM. Examination of these events revealed that lung and renal cancer diagnoses were related to co-incidental imaging for WM staging, whereas all 4 myeloid leukemic and all 13 cases of diffuse B-cell lymphoma events were related to nucleoside analogue therapy. While these studies elude to potential increased surveillance bias, and treatment impact on overall cancer risk comparisons to the general US population, they do not obviate the finding that WM patients may be at an increased cancer risk since 63% of all cancer events occurred before the WM diagnosis. Importantly, these data also herald the need for closer surveillance for other cancers in the context of good primary care practice, but also for cancers of the genitorurinary tract, lung, thyroid, and melanoma. The results also denote an increased risk for myeloid leukemia and aggressive lymphoma following nucleoside analogue treatment, as was also shown in the study by Leleu et al.[25]

As part of these efforts, we also examined malignancies in first- and second-degree kin of patients with WM. We observed no differences in the number of patients with ≥ 1 or more kin with a solid cancer, nor in the types of solid cancers occurring in kin when WM patients were stratified by familial subtype. Unexpectedly, we observed a significant increase in the number of myeloid leukemic events in the kin of patients with familial WM, whose stratification was based on the presence of B-cell malignancies in their family. These studies suggest that a common hematopoietic stem cell defect may predispose to lymphoid as well as myeloid lineage malignancies in these patients and warrants further examination.

In summary, these data suggest that WM patients have a higher incidence of other cancers, with specific cancer clustering based on familial predisposition to WM.

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