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Editorial

Among the Company That Gout Keeps, Is Cancer on the List?

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Over the last 20 years, there has been tremendous growth in understanding the multifaceted aspects of gout. These developments in research span the gamut from elucidating mechanisms by which urate crystals trigger cellular inflammation, to an exciting expansion of available therapeutic modalities to manage gout.[1,2,3,4,5] Concomitantly, we have learned a great deal regarding the genetic contribution to gout susceptibility, while simultaneously observing an amplification in the epidemiology of gout, including newly appreciated risk factors for incident and prevalent disease.

Notably, in the 1960s through the 1990s, the approach to treating gout remained quite constant. For decades, acute attacks of gout were managed with either nonsteroidal antiinflammatory drugs, corticosteroid agents, or colchicine, or with a combination thereof.[6,7,8] In fact, these approaches remain applicable today. Allopurinol, an inhibitor of xanthine oxidase, and probenecid, a uricosuric agent, both act to lower serum uric acid to prevent gout recurrence. However, in the first 20 years of this century, several new kids have emerged on the block. A second xanthine oxidase inhibitor (febuxostat) is in hand.[3] Further, for those with contraindications to frontline acute agents, several interleukin-1 antagonists (canakinumab, rilonacept, and anakinra) have been studied and are seemingly available for off-label use.[5,9] For patients refractory to conventional urate-lowering strategies, an entirely new class of therapy was introduced when a mammalian recombinant uricase conjugated to polyethylene glycol (PEG) was brought to market. This PEGylated uricase, or pegloticase, represents an absolute game changer in the management of patients with severe refractory polyarticular tophaceous gout.[4] In addition, another novel drug class that directly inhibits the renal epithelial urate transporter (lesinurad) transiently entered the marketplace. Clearly, the range of gout therapy has expanded substantially.

In tandem with major advances in gout pathogenesis and therapeutics, there has been transformational growth addressing the epidemiology of gout. It seems remarkable that from 1960 to 1990—not so long ago—there was a relative paucity of published observational cohorts, so vital to appreciate the burden of gout and to ascertain demographic and health status attributes predictive of incident gout.[10,11] Yet in the last 20 years, there has been an explosion of cross-sectional surveys, observational cohorts, and case-control and randomized clinical trials, all of which have added substantially to the epidemiology literature.

From the Framingham Heart Study, a half-century ago, we were apprised about a distinct distribution-by-sex of serum uric acid, with higher average values observed among men than women.[10] We were informed that higher serum levels of uric acid during young and mid-adult life were related to the timing of gout. Those with higher levels experienced a younger mean age at disease onset. In both men and women, there was a dose-response association between urate levels and incidence of gout and nephrolithiasis.[10] Further, the Normative Aging Study in Boston reinforced the notion of a dose-response association between serum uric acid level and gout incidence.[11] BMI, hypertension, and cholesterol were similarly related to incident gout.[11] Further, the Johns Hopkins Precursors Study demonstrated that BMI at age 35, as well as BMI change from the early 20s until age 35, predicted gout development.[12]

Thereafter, we learned from The Health Professionals Follow-up Study and The Nurses' Health Study how dietary components mediate gout risk.[13,14] Intake of meat and seafood was related to incident gout.[13] We also discovered how consumption of beer, but not of wine, as well as of fructose-rich beverages (including sugar sweetened soft drinks and orange juice), heightened the risk to develop gout, whereas coffee consumption was associated with a reduction in risk.[13,14] We found out how cutaneous psoriasis and psoriatic arthritis are both predictive of future gout, and how gout, in turn, is predictive of future hip fracture.[15]

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Data from the cross-sectional National Health and Nutrition Examination Surveys in the United States, a definitive resource reflecting the health of the nation, indicate that the metabolic syndrome, and its component parts, including elevated blood pressure, high levels of cholesterol and triglycerides, and diminished levels of renal function, are related to greater prevalence of gout.[16,17] Further, obstructive sleep apnea was studied and found to be associated with gout.

Though perhaps not widely recognized, and distinct from the aforementioned gout comorbidities, a putative association between malignant disorders and gout has been the focus of medical reports for decades. Notably, in the clinical realm, this relationship has been well known to medical students and house officers alike, and not merely the purview of rheumatologists and oncologists. This likely stems from the tight linkage of induction chemotherapy for lymphoma and its propensity to induce tumor lysis. In this disorder, hyperuricemia, hyperkalemia, and hyperphosphatemia precipitate azotemia and uric acid nephropathy.[18] These clinical features may also follow induction therapy for acute leukemia and may even precede the initiation of chemotherapy when faced with a large tumor burden, as when intraabdominal tumors contribute to extrinsic ureteral compression, thereby impairing renal function. The latter mechanism is distinct from uric acid deposition in the renal parenchyma.

However, in the absence of the mediating effect of chemotherapy, are cancer and gout associated with each other? Moreover, if the relationship exists, what is the directionality of the association? Does gout induce future cancer, or does malignancy (with its proliferation of the malignant clone) induce hyperuricemia and subsequent gout? This concept has engendered scientific inquiry for quite some time. It turns out that even in the first half of the 20th century, an astute clinician at Charing Cross Hospital focused on the intersection of gout, splenomegaly, and immature circulating blood cells: 5 patients had definite polycythemia.[19] Dr. Hickling observed in London that among 9 informative patients, 4 developed gout prior to the overt onset of their hematologic disorder, whereas the other 5 first experienced attacks of gout only 1–11 years after detection of splenomegaly.[19]

Thereafter, in the mid-20th century, Dr. Yü at Mt. Sinai Hospital elaborated in this area by highlighting his experience with 42 secondary cases of gout, attributed to either underlying polycythemia vera or myeloid metaplasia.[20] In this New York City series, gout was reported to have "followed in the wake of active polycythemia," and "developed during the transition from active polycythemia to the myelofibrotic stage" or "during the stage of advanced myeloid metaplasia".[20] However, this report did not inform whether gout can precede the clinical expression or manifest concurrently with the onset of these myeloproliferative disorders. To truly elucidate this relationship, the field would benefit from large population-based cohorts in which the incidence of cancer among those with, compared to those without, gout was compared.

It is within this framework that we read in this issue of *The Journal of Rheumatology* how Lee, *et al* delved further into the gout-malignancy connection.[21] Utilizing the Korean Health Insurance Service database, persons newly diagnosed with gout between 2003 and 2007, aged 41 to 55 years, were followed prospectively, as were age- and sex-matched controls. The authors sought to ascertain whether antecedent gout was related to a heightened risk to develop cancer in Korea. Further, the comparison group was selected from the same calendar year as those diagnosed with gout, with a 1:2 ratio of cases to controls, corresponding to 4176 persons with gout and 8352 controls. The mean age of the participants was 48.8 years, with a full decade of average follow-up time in both groups.

Interestingly, there were 3 major outcomes which differed, in a clinically meaningful and statistically significant fashion, between patients with and without gout. These outcomes—incident cancer, all-cause mortality, and cancer-specific mortality—were each appreciably greater among those with an established diagnosis of gout. Notably, cancer risk was 20% higher, whereas both all-cause and cancer-specific mortality rates were almost 50% higher, among those with antecedent gout. These are impressive and meaningful elevations in risk.[21]

Given the size of the database, the investigators were next able to perform subgroup analyses by cancer type and determined that cancer risk was not uniformly elevated across all cancer types. Specifically, the risk of gastric cancer was 70% higher, and that of head and neck cancer were 85% higher among those with prior gout. In contrast, there was a null association between gout and risk to develop cancer of the esophagus, liver, genitourinary tract, prostate, breast, and female reproductive tract.[21] For completeness, there were other cancer types with apparent associations with gout, yet lacking statistical significance, such as for pancreatic, lung, and thyroid tumors; an estimated 30% reduction in risk was noted for colon cancer but was of borderline statistical significance. Moreover, the cancer type with the highest risk estimate in relation to antecedent gout was hematologic or lymphoid malignancy, with an almost 3-fold elevation among those with gout.

Biologically speaking, it is of conceptual and practical interest to determine the directionality of this association. By nature of the prospective cohort study design, one would presume that gout does in fact predict the development of future malignancy, such as a hematologic malignancy. Moreover, the longer the interval between the diagnosis of gout and the future detection of a tumor, the more one might embrace true causality. Alternatively, however, could a preclinical, asymptomatic background of an evolving hematologic malignancy, not yet clinically manifest, be the reason why gout occurred in the first place? In such a scenario, gout might have declared itself first, only later to be followed by an overt, clinically apparent, and histologically proven malignancy. This scenario might be biologically feasible and most applicable with shorter intervals in time between the onsets of gout and cancer. The biologic basis for this consideration seems plausible given the known predilection for evolving myeloproliferative disorders (with high levels of cellular turnover and accelerated purine metabolism) to induce gout.[20] Unfortunately, in the study by Lee, *et al*,[21] we are not informed about the time interval between the new diagnosis of gout and

the later development of cancer, either in aggregate or by specific tumor type.

What prior data exist to support the notion that gout is a risk factor for cancer? Is there evidence beyond the current observational cohort in Korea to support the notion that gout may be in the causal pathway of carcinogenesis? The answer lies in part with 2 comparable epidemiologic reports in other populations that similarly examined cancer incidence in relation to antecedent gout status. Specifically, in the Swedish nationwide hospital discharge system, there was a 25% higher risk to develop cancer among 16,857 hospitalized patients with gout, during the follow-up period, compared to the Swedish population as a whole.[22] This elevated risk to develop cancer pertained to malignancies of the oropharynx, colon, liver, pancreas, lung, endometrium, kidney, and skin (melanoma). Further, using a comparable approach in Taiwan, an analysis of the National Health Insurance Database identified a modestly elevated risk to develop cancer among those with gout.[23] Yet, whereas a 2-fold increase in risk was observed in univariate analysis, after further adjustment for age and sex, the multivariate HR was markedly reduced to a modest level of 1.15. Further, in site-specific cancers, gout among men was particularly related to prostate cancer (HR 1.71).[23] However, when the analysis was restricted to the subset with highest utilization of emergency room visits, the overall association was, seemingly unexpectedly, nullified.

What might be the pathophysiologic pathway by which gout mediates cancer risk? Some immediate considerations include dietary exposure to alcohol, which is a well-recognized risk factor for gout and a known risk factor for certain cancers (e.g., hepatocellular carcinoma). Are there elements of the metabolic syndrome, including obesity, hypertension, and hyperlipidemia, in the causal pathway to gout development that may in turn mediate cancer risk?[24] These are putative intervening mechanisms to be addressed further in ongoing laboratory and epidemiologic reports.

As the investigative lens continues to focus on uric acid and gout, it is incumbent upon the primary care physician, rheumatologist, cancer biologist, and epidemiologist alike to be educated about the gout comorbidity profile as well as the strength and biologic plausibility of the gout-malignancy connection. In this context, the pages of this issue of *The Journal* inform us clearly and compellingly how the cumulative incidence of cancer differs, and is elevated, among those with gout compared to the general population.[21] Moreover, those with gout experienced a higher rate of cancer-related mortality. This instructive paper illuminates the gout community as to why cancer belongs on the list of comorbidities that gout keeps.

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