Prior cancer and risk of monoclonal gammopathy of undetermined significance: a population-based study in Iceland and Sweden

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Abstract

There is some evidence that a prior cancer is a risk factor for the development of multiple myeloma (MM). If this is true, prior cancer should be associated with a higher prevalence or increased progression rate of monoclonal gammopathy of undetermined significance (MGUS), the precursor of MM and related disorders. Those with a history of cancer might therefore constitute a target population for MGUS screening. This two-part study is the first study to evaluate a relationship between MGUS and prior cancers. First, we evaluated whether prior cancers were associated with having MGUS at the time of screening in the Iceland Screens Treats or Prevents Multiple Myeloma (iStopMM) study that includes 75,422 individuals screened for MGUS. Next, we evaluated the association of prior cancer and the progression of MGUS to MM and related disorders in a population-based cohort of 13,790 Swedish individuals with MGUS. A history of prior cancer was associated with a modest increase in the risk of MGUS (odds ratio=1.10; 95% confidence interval: 1.00-1.20). This excess risk was limited to prior cancers in the year preceding MGUS screening. A history of prior cancer was associated with progression of MGUS, except for myeloid malignancies which were associated with a lower risk of progression (hazard ratio=0.37; 95% confidence interval: 0.16-0.89; *P*=0.028). Our findings indicate that a prior cancer is not a significant etiological factor in plasma cell disorders. The findings do not warrant MGUS screening or different management of MGUS in those with a prior cancer.

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is the asymptomatic precursor of multiple myeloma (MM), Waldenström macroglobulinemia (WM), and other lymphoproliferative disorders (LPD).[1,2] MGUS is common in the general population with a prevalence of 4.2% in subjects over the age of 50 years, but only in 0.5-1.5% per year does the MGUS progress to active malignancy.[2-4] The causes of MM, WM and other LPD are poorly understood but both genetic[5] and environmental[6,7] causes have been implicated. Importantly, because MGUS is the precursor of MM, WM, and related LPD, the etiology of these malignancies would be expected to involve the development or progression of MGUS.

Having cancer increases the risk of a second primary malignancy[8] but MM and WM are usually not considered as second primary malignancies. Theoretically, various factors

could lead to the emergence of MM and WM or other LPD as second primary malignancies. These comprise therapy- and disease-related carcinogenic effects,[9] including immune dysfunction which is critical to the progression of MGUS.[10] Furthermore, there may be shared genetic or environmental factors. There is limited epidemiological evidence that having a solid or myeloid cancer decreases or increases the risk of MM, respectively.[11] Similar, conflicting results have been found in the patterns of cancers in family members of those who have had WM.[12] In contrast, other LPD, in particular chronic lymphocytic leukemia, have been associated with prior cancer. However, this may be due to biased detection of asymptomatic chronic lymphocytic leukemia during follow-up.[13] We are not aware of any studies that have examined the risk of MGUS and its progression in those with a prior cancer.

We were motivated to assess the relationship of prior cancers and the development of MGUS in the unique population-based and screened Iceland Screens, Treats, or Prevents Multiple Myeloma (iStopMM) study cohort and the progression of MGUS in a large population-based MGUS registry from Sweden with up to 36 years of follow-up. By doing so we aimed to improve our understanding of the etiology of MGUS and its progression, and thereby the pathways that lead to MM, WM, and other LPD. Furthermore, cancer is common in the general population with more than 40% of individuals estimated to develop cancer during their lifetime.[14] If those who have prior cancer have elevated risks of MGUS or its progression, they may be a target population for MGUS screening.

Methods

The study included two cohorts. The first cohort was acquired from the iStopMM study, a population-based screening study for MGUS. In total, 75,422 Icelanders ≥40 years old (51% of the total eligible population) were screened by serum protein electrophoresis and free light chain assay. Those with a prior history of MM, WM or other LPD were excluded. The study has been described elsewhere.[15] The second cohort was acquired from a population-based MGUS registry including 13,790 subjects diagnosed in Sweden between 1987 and 2013. This registry has also been described in greater detail elsewhere.[16]

Prior and subsequent cancer diagnoses were acquired from the Icelandic and Swedish cancer registries, which have both been shown to have high accuracy and timeliness.[17,18] Additional diagnoses of subsequent WM and chronic lymphocytic leukemia were acquired from the Swedish Patient Registry.[19] Prior cancers were analyzed as any cancer, solid cancers, non-melanoma skin cancer, and myeloid cancer (*Online Supplementary Table S1*). The timing of prior cancers was grouped as <1, 1-5, 5-10, and >10 years before screening.

For the statistical analysis, we first assessed the risk of MGUS at screening after a prior cancer diagnosis in the iStopMM study cohort using a case-control design. Logistic regression was used to estimate odds ratios (OR) for MGUS for those with a prior cancer diagnosis with stratification by cancer subtype, by the timing of the prior cancer, and by MGUS isotype, adjusting for sex and age as a non-linear variable using four-knot restricted cubic splines. Second, we assessed the association of a prior cancer before MGUS diagnosis in the Swedish cohort, and subsequent MGUS progression. Because MGUS can be a temporary diagnosis before the diagnosis of MM or related disorders, participants were followed from 3 months after the diagnosis of MGUS to the MGUS progression or censoring at death and end of follow-up. To account for the competing risk of death we used Fine-Grey survival models to estimate sub-distribution hazard ratios (sHR) and adjusted for age and sex.

The study was approved by the Icelandic Science Ethics Committee and the Regional Ethics Board of Stockholm.

Results

A total of 74,654 participants in the iStopMM study were included, of whom 3,579 had MGUS. At total of 9,891 participants had at least one of a total of 10,598 prior cancer diagnoses, of whom 70%, 29%, and 1% had solid, non-melanoma skin, and myeloid cancer, respectively (Table 1). A prior history of cancer was associated with a 10% increased risk of developing MGUS overall (OR=1.10; 95% confidence interval (CI): 1.00-1.20) (Figure 1). This difference was only observable for prior cancer within a year before screening for MGUS overall and non-IgM MGUS (OR=1.36; 95% CI: 1.07-1.74 and OR=1.57; 95% CI: 1.18-2.08) (Figure 2). No specific prior cancer category or solid cancer subtype was found to be associated with MGUS at screening except the combined category of hepatic, biliary, and pancreatic cancer as well as cancers of the urinary tract (OR=2.59; 95% CI: 1.39-4.48 and OR=1.27; 95% CI: 1.00-1.61, respectively) (*Online Supplementary Table S2*). A sensitivity analysis was performed to rule out that this effect was driven by those who had previously known MGUS before screening, for whom the date of MGUS screening was moved to the date of MGUS diagnosis. This did not affect the results (*data not shown*). Of the 13,790 participants in the Swedish cohort, 1,834 (13%) had a prior cancer diagnosis before MGUS and 1,658 (12%) subsequently experienced MGUS progression (Table 2). Those who had any prior cancer did not have a significantly increased risk of MGUS progression overall (sHR=1.14; 95% CI: 0.97-1.34; *P*=0.11) but those with a prior myeloid cancer had a significantly lower risk of MGUS progression (sHR=0.37; 95% CI: 0.16-0.89; *P*=0.028) (Figure 3). However, only five individuals with a prior history of myeloid cancer progressed during the study period. There was no statis-

Table 1. Baseline characteristics of the iStopMM cohort.

	Without MGUS	With MGUS	Subtype of MGUS			
			Non-IgM	IgM	Biclonal	Light chain
Participants, N	71,075	3,579	2,257	704	304	314
Male, %	45	54	52	55	59	60
Age in years, median (IQR)	61 (52-69)	69 (62-77)	69 (60-76)	71 (64-79)	73 (65-80)	68 (59-76)
Prior cancer,* N (%)	9,176 (12.9)	715 (20.0)	437 (19.4)	157 (22.3)	69 (22.7)	52 (16.6)
Solid cancer#	6,837 (9.4)	527 (13.9)	324 (13.5)	116 (15.2)	49 (15.2)	38 (11.7)
Non-melanoma skin cancer#	2,854 (3.9)	249 (6.5)	152 (6.3)	58 (7.6)	24 (7.4)	15 (4.6)
Myeloid cancer#	119 (0.2)	12 (0.3)	7 (0.3)	3 (0.4)	2 (0.6)	0 (0.0)
Time from prior cancer, N (%)						
<1 year	919 (1.3)	74 (2.1)	53 (2.3)	10 (1.4)	7 (2.3)	4 (1.3)
1-5 years	2,266 (3.2)	163 (4.6)	101 (4.5)	38 (5.4)	14 (4.6)	10 (3.2)
5-10 years	2,287 (3.2)	171 (4.8)	112 (5.0)	34 (4.8)	14 (4.6)	11 (3.5)
>10 years	3,704 (5.2)	307 (8.6)	171 (7.6)	75 (10.7)	34 (11.2)	27 (8.6)

Note that some participants had more than one prior cancer of different subtype. *Number of individuals with at least one prior cancer and as a ratio of all individuals in that group. #Number of prior cancer diagnoses of that subtype and as a ratio of all cancers. iStopMM: Iceland Screens, Treats, or Prevents Multiple Myeloma; MGUS: monoclonal gammopathy of undetermined significance; IQR: interquartile range.

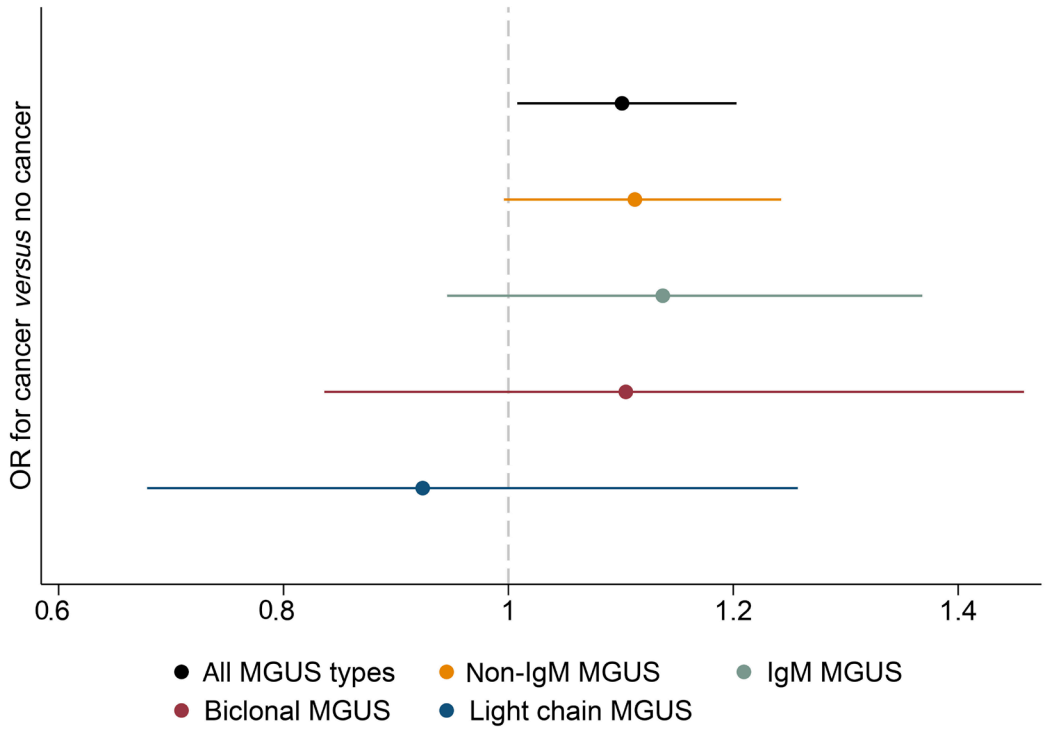

Figure 1. The odds ratios of monoclonal gammopathy of undetermined significance and its subtypes for those with a prior cancer diagnosis as compared to those without a prior cancer diagnosis. OR: odds ratio; MGUS: monoclonal gammopathy of undetermined significance; IgM: immunoglobulin M.

tically significant difference in progression risk overall for those with any subtype of solid or myeloid cancer, except in the case of myeloproliferative neoplasms for which those with a prior history had a lower risk of MGUS progression (*Online Supplementary Table S3*).

Discussion

In this study based on two high-quality large population-based cohorts including close to 100,000 individuals, we found that a prior cancer is associated with a 10% increase in the risk of having MGUS later in life. Prior cancer is therefore not a clinically significant risk factor for MGUS. Furthermore, this increased risk of MGUS was only observed for prior cancers less than a year before screening and because MGUS is often present for decades[2,3] without progressing, it is unlikely that this is a causative association. Potential explanations include common risk factors, cytotoxic therapy lowering the polyclonal background and revealing an M protein, or reverse causality. Another potential explanation is exogenous monoclonal antibodies. However, the pattern of prior cancer types associated with MGUS is not consistent with that hypothesis. These findings indicate that MGUS is not an etiological factor in the development of MGUS and that MGUS screening in individuals with prior cancer is not warranted.

A prior history of cancer was not associated with an in-

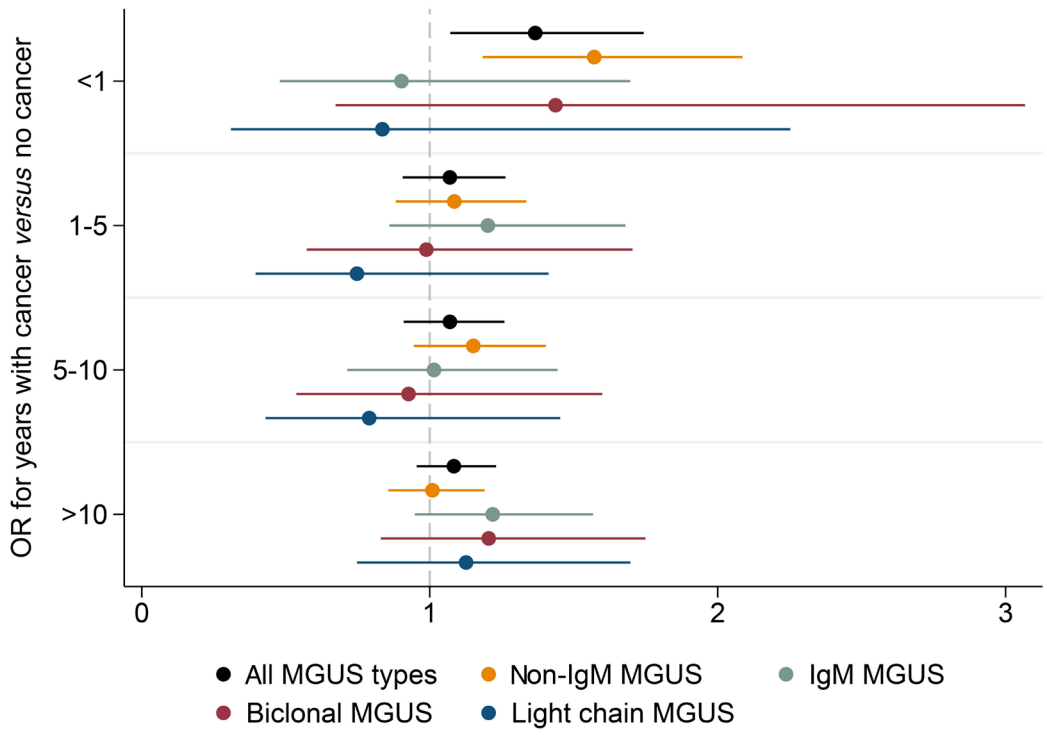

Figure 2. The odds ratios of having monoclonal gammopathy of undetermined significance for those with a prior cancer compared to those without a prior cancer by the number of years passed since the diagnosis of the prior cancer and the subtype of gammopathy. OR: odds ratio; MGUS: monoclonal gammopathy of undetermined significance; IgM: immunoglobulin M.

Table 2. Baseline characteristics of the Swedish cohort included in the analysis for progression of monoclonal gammopathy of undetermined significance.

	Prior cancer	No prior cancer
Participants, N	1,834	11,956
Male, %	56	50
Age in years, median (IQR)	76 (68-81)	71 (62-79)
Year of diagnosis, %		
1987-1995	9	23
1996-2003	33	34
2004-2013	59	43
Potential follow-up in years*	3.6	5.7
Progression, N (%)	171 (9.3)	1,487 (12.4)
Multiple myeloma	93 (5.1)	866 (7.2)
Waldenström macroglobulinemia	34 (1.9)	295 (2.5)
Amyloidosis	11 (0.6)	112 (0.9)
Other LPD	33 (1.8)	214 (1.8)

*As determined by the Kaplan-Meier estimator with censoring as the outcome. IQR: interquartile range; LPD: lymphoproliferative disorders.

creased risk of MGUS progression overall. However, surprisingly, a prior myeloid cancer was associated with a significant reduction in the risk of MGUS progression. It is important to note that many myeloid cancers, particularly myeloproliferative disorders, often do not require therapy[20] and that serum protein electrophoresis is often performed during the work-up of hematologic disorders in Sweden. Those individuals with MGUS and a prior myeloid cancer may therefore have had a higher rate of low-risk MGUS. Our interpretation of the results is that a prior history of cancer is not meaningfully associated with MGUS progression. These findings indicate that a prior history of cancer should not affect the management of MGUS, except in the setting of goals-of-care in relation to the general health of the affected individual.

No prior cancer subtype appeared to drive the increased risk of MGUS observed but an increased risk was seen in those with hepatic, biliary, and pancreatic cancers and cancer of the urinary tract. Importantly, this was in the setting of multiple comparisons and these associations may have been spurious. The findings are in contrast to those of a population-based study by Langseth *et al.* from Norway in which the authors found that solid tumors were associated with a lower risk of MM. Furthermore, they found myeloid cancer to be associated with a higher risk of MM, the opposite finding of our study.[11] In contrast to this prior study, the current study is based on a screened cohort and long-term follow-up of a large MGUS cohort providing an unbiased epidemiological view of the pathogenesis of MM and related disorders. Furthermore, the prior study was affected by important potential biases including detection of low-grade myeloproliferative disorders in the work-up leading to the diagnosis of MM (a phenomenon we have observed in diabetes[21]) and misclassification of MM bone lesions as solid tumor metastasis. It is therefore likely that the current study reflects the true underlying association of prior cancers and MM more accurately.

This study has several strengths. First, the risk of MGUS was assessed using screening in the iStopMM study cohort. This avoided the selection bias that affects most other MGUS cohorts in which MGUS has been detected during the work-up for other disorders.[22] Secondly, the risk of MGUS progression was assessed in a large population-based MGUS cohort with up to 36 years of follow-up. Finally, the Icelandic and Swedish cancer registries are very high quality leading to accurate determination of prior cancers and subsequent MGUS progression.[17-19]

The study also has important limitations. Firstly, because MGUS is asymptomatic and can be present for decades without developing into malignancy, the direction of the

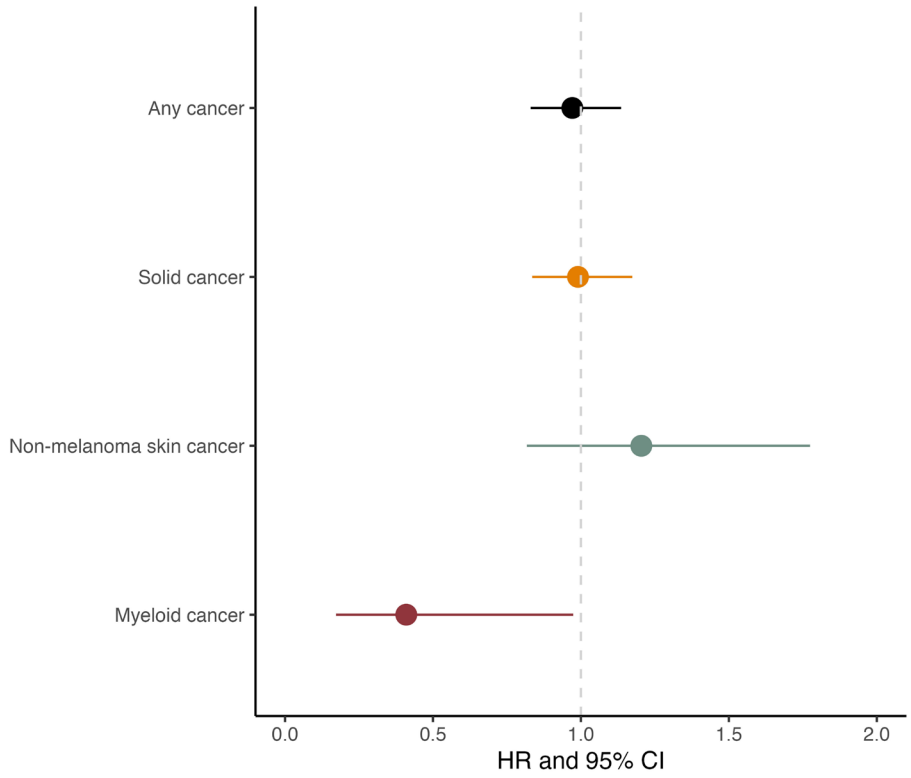

Figure 3. A forest plot of hazard ratios for risk of progression of monoclonal gammopathy of undetermined significance for those with any type of prior cancer and by prior cancer subtype. HR: hazard ratio; CI: confidence interval.

observed association is unclear. Secondly, although the total number of prior cancers was high, some cancer subtypes remained rare, precluding the detection of any rare cancer subtype-specific risks. However, due to the size of the study such associations are unlikely to hold much clinical significance. Thirdly, the study data did not include many prior cancers after the advent of immuno-oncology and targeted therapies[23,24] which may affect the risk of MGUS or its progression in ways different from those of conventional therapies. Fourthly, the study populations are genetically and ethnically homogenous which may affect the nature of the prior cancers and may limit the generalizability of the results. Finally, all participants in the iStopMM study had to consent to MGUS screening and those with a prior cancer might be more or less likely to want to undergo screening; however, effect is non-differential between the groups in the analysis and should not have affected the overall result.

In conclusion, in this large study based on two complementary population-based cohorts, we found that a recent history of cancer was associated with a modest increase in the prevalence of MGUS. However, prior cancer was not associated with the risk of MGUS progression. This association is unlikely to be causal or to be of clinical significance. Based on these findings we conclude that MM, WM, and other LPD preceded by MGUS are not significant second primary malignancies. The findings do not warrant surveillance of those with prior cancer for plasma cell disorders or differential management of MGUS in those with a prior cancer. The study provides robust evidence against the hypothesis that prior cancers and associated therapies cause plasma cell disorders and can help guide the attention of investigators towards other potential risk factors that could improve our understanding of the pathogenesis of plasma cell disorders and lead to potential avenues of prevention.

Disclosures

MB has been part of a grant committee for Incyte; sat on educational program committees for Roche, Pfizer, and Bristol-Myers Squibb; acted as a consultant or advisor for Janssen-Cilag and Schain Research; and received a research grant from Takeda. MH has received research grants from Amgen, GlaxoSmithKline and Daiichi Sankyo Company; and has acted as a consultant or advisor for Bristol-Meyers Squibb, Curio Science, GlaxoSmithKline, and Intellisphere. SH is currently employed at The Binding Site Ltd. OL has received research funding from the National Cancer Institute/ National Institutes of Health, Food and Drug Administration, Leukemia & Lymphoma Society, Rising Tide Foundation, Multiple Myeloma Research Foundation, International Myeloma Foundation, Paula and Rodger Riney Foundation, Tow Foundation, Myeloma Solutions Fund, Perelman Family Foundation, Amgen, Celgene, Janssen, Takeda, Glenmark, Seattle Genetics, and Karyopharm; has received honoraria for scientific talks or participated in advisory boards for Adaptive, Amgen, Binding Site, Bristol-Meyers Squibb, Celgene, Cellectis, Glenmark, Janssen, Juno, and Pfizer; and has sat on independent Data Monitoring Committees for Takeda, Merck, and Janssen. SYK has received research funding from Amgen and Celgene; and has sat on an independent Data Monitoring Committee for Jansen.

Contributions

SR conceived the study and its design with further input from ST, IS, EE, JTO, TEL, and SYK. Data were analyzed by SR and ES. ITu, MB, and SYK collected data from Sweden. GKG, AO, and JKS curated data with supervision from TA. SYK supervised the project and the iStopMM study. SR, ST, IS, EE, JTO, TEL, BV, PTO, BAA, MS, IO, ITh, MH, BGMD, SH, OL, TJL, and SYK are part of the iStopMM team of investigators. All co-authors had access to and edited the manuscript.

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Data-sharing statement

Current approvals do not allow for sharing of the underlying study data. However, data may be shared with other investigators pending the review of the iStopMM investigators and the Icelandic Scientific Ethics Committee.

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