Respiratory tract infections in the pathway to multiple myeloma: a population-based study in Scandinavia

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Encounter with infectious antigens has been proposed to initiate the cascade of events associated with progression from premalignancy (monoclonal gammopathy of undetermined significance, MGUS) to multiple myeloma (MM). We conducted a population-based case-control study to evaluate risk of developing MM associated with a personal history of various respiratory tracts infections occurring >1 year prior to MM. Inpatient (1977-1997) and outpatient (1994-1997) diagnoses were obtained for all MM patients (n=4,476) diagnosed in Denmark (1977-1997) and 16,727 matched controls. A personal history of pneumonia was associated with a 1.6-fold (95%CI 1.3-2.0) increased risk of MM; the elevated risk was restricted to 1-4.99 years prior to the diagnosis of MM (OR=1.7,95%CI 1.3-2.2). Individuals with two and three or more previous episodes of pneumonia had a 1.7-fold (95%CI 1.0-3.0; *p*=0.05) and a 1.5-fold (95%CI 0.6-3.9) elevated MM risk, respectively. Pneumonia could be a trigger to the development of MM or a manifestation of immune disturbances in late-stage MGUS.

Key words: multiple myeloma, etiology, pneumonia, infectious agents, MGUS.

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Multiple myeloma (MM) is a malignant clonal neoplasm of plasma-cells characterized by an overproduction of large amounts of monoclonal immunoglobulins. Clinical symptoms may include bone pain, infections, hypercalcemia, renal failure, cytopenias, or other abnormalities. MM is often preceded by a precursor condition, monoclonal gammopathy of undetermined significance (MGUS);[1-3] however, it remains unclear whether MGUS precedes all cases of MM or whether MM can arise *de novo* without preceding MGUS.[4-6] To date there are no established risk factors for MGUS and MM. Approximately 50% of patients with MGUS have primary translocations in the clonal plasma-cells involving the immunoglobulin heavy chain (IgH) locus on chromosome 14q32,[1,7] which is considered to be of importance for initiation and support of clonal proliferation.[5,6,8] It has been proposed that infections could be the precipitating event for these translocations, and that the translocations likely occur during IgH switch recombination or somatic hypermutation.[7] The pathogenesis of MGUS without evidence of IgH translocations is currently unknown.

Long-term follow-up of patients with MGUS reveals a constant approximately 1% annual risk of developing MM or, to a lesser extent, other lymphoproliferative malignancies.[2,9] A stable risk of progression regardless of duration of antecedent MGUS has been proposed[10] to reflect the second hit in a random, two-hit genetic model of malignancy.[9] The specific second hit that initiates the cascade of events associated with progression is unknown and may be different in non-translocated versus translocated MGUS IgH; in the latter there might be various triggers depending on the partner chromosome involved.[1,4,6-8,10] Initiation mechanisms might include genetic susceptibility, encounter with antigens causing a classical antigen-driven somatic hypermutation process, and/or gene-environment interactions. Based on recent findings, common antigens involved in the pathogenesis of MM are less likely to be of the auto-antigen type,[11] and more likely represent extrinsic environmental factors. Interestingly, associations between MM and a personal history of pneumonia and other infections have been observed in case reports and small studies.[12-14]

The objective of this study was to quantify the risk of MM following various respiratory tract infections, including pneumonia. We identified airway infections utilizing hospital discharge records for 4,476 population-based MM patients and more than 16,000 frequency-matched controls in Denmark over a 20-year-period.

Design and Methods

All incident MM patients diagnosed between 1977-1997 were collected from the nationwide Danish Cancer Registry. Four malignancy-free controls per patient were randomly chosen from the Danish Central

Population Registry,[15] matched to the patients by sex, year of diagnosis, year of birth, and county. Approval was obtained from the National Institute of Health institutional review board for these studies. Informed consent was waived because we had no contact with study subjects.

Patients and controls were linked with the population-based Danish Inpatient (1977-1997) and Outpatient (1994-1997) Registers to collect information on discharge listing of any of the following coded (ICD 8th to 10th Revisions) airway infections: tuberculosis, pneumonia, bronchitis, unspecified lower airway infection, laryngitis, unspecified upper airway infection, nasopharyngitis/pharyngitis, sinusitis, otitis media/mastoiditis, and influenza.

We calculated odds ratios (OR) and 95% CI as measures of relative risk using unconditional logistic regression, adjusting for sex, age at diagnosis, and year of diagnosis. Airway infection data were restricted to those infections that occurred more than one year before the diagnosis of MM for patients and their corresponding controls. We further examined the association between MM risk and number of events (1, 2, and ≥3) and time from discharge listing a defined airway infection until the diagnosis of MM (1-4.99, and ≥5 years' latency). Furthermore, we analyzed the associations for patients with early diagnosis (<65 years) and late diagnosis (≥ 65 years) of MM; we also stratified our analyses by sex. In separate analyses, we examined the association between MM risk and airway infections occurring less than one year before the diagnosis of MM for patients and their corresponding controls.

Results and Discussion

A total of 4,476 MM patients and 16,727 matched controls were included (Table 1). We found 207 patients and 648 controls with a history of airway infections. Among affected patients, the percentage of individuals with a history of 1, 2, and ≥3 separate episodes of defined airway infections was 68%, 18%, and 14%, respectively. For controls the corresponding numbers were 66%, 20%, and 14%.

In analyses restricted to infections that occurred more than one year before the diagnosis of MM for patients and their corresponding controls, we found significantly increased risk of MM associated with a personal history of pneumonia (OR=1.6, 95% CI 1.3-2.0) (Table 2). Furthermore, in analyses stratified by latency, a significant 1.7-fold (95% CI 1.3-2.2) and a borderline 1.4-fold (95% CI 0.96-2.0) increased risk of MM was observed in the latency intervals of 1-4.99 years and ≥5 years, respectively. When we considered the two latency periods in a multivariate model, the 1-4.99 year latency interval remained independently associated with an elevated MM risk (OR=1.5, 95% CI 1.1-1.9), but the asso-

Table 1. Characteristics of multiple myeloma patients and controls.

Variable	*Patients*	*Controls*
Total number	4,476	16,727
Age in years, median (interquartile range)	70 (61-77)	70 (61-77)
Age group, n (%)		
<65 years	2,175 (49)	7,586 (45)
≥65 years	2,301 (51)	9,141 (55)
Sex, n (%)		
Male	2,438 (54)	9,117 (55)
Female	2,038 (46)	7,610 (45)
Calendar year, median (interquartile range)	1988 (1983-1993)	1988 (1983-1993)

Table 2. Association between multiple myeloma and a personal history of airway infections.*

Airway infection/category	*Patients*	*Controls*	*OR*	*(95% CI)*
Lower airways				
Bronchitis	111	386	0.9	(0.7-1.2)
Lower airway infection, unspecified	13	54	0.9	(0.5-1.6)
Pneumonia, overall	121	290	*1.6*	*(1.3-2.0)*
Pneumonia, by subgroup				
Age at MM diagnosis				
<65 years	12	20	*2.3*	*(1.1-4.7)*
≥65 years	109	270	*1.5*	*(1.2-1.9)*
Sex				
Male	56	154	1.4	(1.0-1.9)
Female	65	136	*1.8*	*(1.3-2.4)*
Number of infections				
1	98	237	*1.6*	*(1.2-2.0)*
2	17	38	1.7	(1.0-3.0)
≥3	6	15	1.5	(0.6-3.9)
Latency interval° (years)				
1-4.99	85	191	*1.7*	*(1.3-2.2)*
≥5	42	114	1.4	(0.96-2.0)
Upper airways, nasal, sinus, and middle ear				
Laryngitis	3	17	0.7	(0.2-2.3)
Nasopharyngitis/pharyngitis	3	6	1.9	(0.5-7.5)
Upper airway infection, unspecified	7	27	1.0	(0.4-2.2)
Sinusitis	8	20	1.5	(0.7-3.4)
Otitis media/mastoiditis	8	32	0.9	(0.4-2.0)
Other				
Influenza	11	27	1.5	(0.7-3.1)
Tuberculosis	6	35	0.6	(0.3-1.5)

*OR: odd ratio; CI: confidence interval. OR were adjusted for age, calendar time of MM diagnosis, and sex. Italic entries have p values <0.05; *: including only events >1 year prior to the diagnosis of MM; °: time from discharge listing a defined airway infection until diagnosis of MM. Since outpatient data were only available from the start of 1994, we examined the association separately for infections diagnosed 1977-1993 and 1994-1997; risk estimates were virtually the same. Because subjects could contribute pneumonia episodes to more than one latency interval, the latency totals do not sum to the total number of people with pneumonia.*

ciation in the ≥5 years latency interval was attenuated and no longer statistically significant (OR=1.2, 95% CI 0.8-1.7). Among persons with two or three prior episodes of pneumonia, we found a borderline 1.7-fold (95% CI 1.0-3.0; p=0.05) and a non-significant 1.5-fold (95% CI 0.6-3.9) increased risk of MM, respectively. The association between MM and any history of prior pneumonia did not differ according to the age at onset of MM (p=0.45) or sex of the patients (p=0.96) (Table 2).

In a separate analysis restricted to the period less than 1 year before the diagnosis of MM, we observed a highly significantly increased risk of MM associated with pneumonia (OR 8.7, 95% CI 6.7-11.4; 176 MM patients versus 79 controls). We found no association between other airway infections and MM risk, but the results for most infection events were based on small numbers (Table 2). We observed that a personal history of pneumonia in the 1-4.99 year latency interval was associated with a significant 1.7-fold increased risk of MM. This finding suggests that pneumonia might be a potential late trigger for the development of MM.[1,4,9,10] Alternatively, pneumonia could be a manifestation of immune disturbances of undetected MM or late-stage MGUS. Indeed, we could not entirely rule out an association between pneumonia and MM risk at a longer latency. Future studies on MGUS patients, including information on repeated consecutive monoclonal protein assays in combination with other laboratory markers (such as bone marrow biopsy results and serum analyses of β-2-microglobulin, albumin, free κ and λ light chains, C-reactive protein, and interleukin-6) and clinical variables (including inpatient and outpatient data regarding respiratory tract infections), are needed to explore the underlying mechanisms of our findings.

There is no compelling biological reason that the risk of MM associated with airway infections should differ depending on sex or on the age of diagnosis at MM. However, given that more males than females have MM and that the incidence of both MM and pneumonia increases with age, we conducted exploratory analyses stratified by sex and age. We found that the risk of MM associated with airway infections did not differ significantly depending on sex (p=0.96) or age of diagnosis at MM (p=0.45). Although recurrent infections are frequently associated with MM as part of the natural history of the disease,[16-18] the presence of infection at the time of diagnosis of the malignancy or as the initial clinical presentation has been reported to be rare.[12,13] We observed that approximately 3% of all MM patients diagnosed in Denmark during the 20-year study-period had been hospitalized due to pneumonia in the preceding year. Even though the proportion of MM patients affected by pneumonia was relatively small, the risk was nonetheless substantially higher than that in controls (OR=8.7). Part of this increased risk might also reflect a diagnostic evaluation for MM following hospitalization for pneumonia.

We used a register-based case-control design, which provided a very large population-based sample, minimized recall-bias, and allowed us to evaluate risk according to age and sex. An important limitation was the unavailability of outpatient data for most years (1977-1993), which led to substantial under-ascertainment of upper airway infections. Although a history of respiratory tract infections was assessed among matched controls using the same hospital discharge registries, bias might theoretically have been introduced if subjects who were predisposed to develop MM also responded more severely to infections (leading to hospitalization). We also lacked information on MGUS status among patients and controls, which prevented us from examining the time relationship between MGUS and airway infections. Finally, the lack of information on potential confounding exposures was a limitation; however, because there are no established risk factors for MM, it is unlikely that this lack introduced substantial bias in our results.

In summary, a personal history of pneumonia was a predictor for risk of MM, particularly among individuals with episodes of pneumonia in the 5 years preceding MM. Our results suggest that pneumonia might be a potential late trigger for MM development or a manifestation of immune disturbances of late-stage MGUS. Future studies examining underlying mechanisms of the observed findings may provide insights into the etiology of MM.

OL and EAE designed the study; LM, GG, and LRG obtained data; JSR, OL, and EAE analyzed data; OL initiated this work and wrote the report. All authors were involved in the interpretation of the results, read, gave comments, and approved the final version of the manuscript. JSR, OL, and EAE had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Each author declares he/she has no conflict of interests relevant to this paper.

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