Autoimmunity and the risk of myeloproliferative neoplasms

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ABSTRACT

The causes of myeloproliferative neoplasm (MPN) are unknown. We conducted a large population-based study including 11,039 myeloproliferative neoplasm patients and 43,550 matched controls with the aim of assessing the associations between a personal history of a broad span of autoimmune diseases and subsequent risk of myeloproliferative neoplasm. We found a prior history of any autoimmune disease to be associated with a significantly increased risk of myeloproliferative neoplasms (odds ratio (OR)=1.2; 95% confidence interval (CI) 1.0-1.3; *P*=0.021). Specifically, we found an increased risk of MPNs associated with a prior immune thrombocytopenic purpura (2.9; 1.7-7.2), Crohn's disease (1.8; 1.1-3.0), polymyalgia rheumatica (1.7; 1.2-2.5), giant cell arteritis (5.9; 2.4-14.4), Reiter's syndrome (15.9; 1.8-142) and aplastic anemia (7.8; 3.7-16.7). The risk of myeloproliferative neoplasms associated with prior autoimmune diseases is modest but statistically significant. Future studies are needed to unravel the effects of these autoimmune diseases themselves, their treatment, or common genetic susceptibility.

Key words: myeloproliferative neoplasms, autoimmune diseases, polycythemia vera. essential thrombocythema, primary myelofibrosis, Crohn`s disease, immune thrombocytopenic purpura, giant cell arteritis, polymyalgia rheumatica, aplastic anemia.

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Introduction

Chronic myeloproliferative neoplasm, including polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), are termed myeloproliferative neoplasms (MPNs).[1] Biologically, they are thought to be stem cell-derived clonal proliferative myeloid malignancies whose shared and diverse phenotypic characteristics can be attributed to dysregulated signal transduction because of acquired somatic mutations.[2] Myeloproliferative neoplasms are uncommon tumors with yearly incidence rates of 2.3 in 100,000 in the United States.[3] Myeloproliferative neoplasms primarily affect older adults and can have a variable clinical presentation.[4-7]

The underlying causes of myeloproliferative neoplasms are largely unknown. A mutation in the gene for *Janus kinase 2*, (*JAK2*)V617F, is present in most erythropoietin-independent erythroid colonies in polycythemia vera.[8] The mutation is present in 95% of polycythemia vera patients and in approximately 50% of essential thrombocythemia and primary myelofibrosis patients.[2] However, other primary pathogenetic mutations have been hypothesized.[9] A role for hereditary factors in the etiology of myeloproliferative neoplasms has been suggested. We recently performed a large population-based study including more than 11,000 MPN patients and found 5-7 fold risk of developing myeloproliferative neoplasms among first-degree relatives of MPN patients, compared to first-degree relatives of controls.[4] Furthermore, recent studies suggest that the *JAK2* gene is a susceptibility gene for myeloproliferative neoplasms both in the germline and somatically.[10-12]

A personal history of autoimmune diseases has been consistently associated with an increased risk of lymphomas.[13, 14] Interestingly, there are emerging data to suggest that autoimmunity could play a role in the development of myeloid malignancies such as acute and chronic myeloid leukemias.[15] However, due to the rarity of myeloproliferative neoplasms, there are only sparse data available regarding the association between autoimmune diseases and risk of developing myeloproliferative neoplasms.[15,16]

To improve our understanding on this topic, we conducted a large population-based study including more than 11,000 MPN patients and more than 43,000 matched controls. The aim of our study was to assess the associations between a

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personal history of a broad span of autoimmune diseases and subsequent risk of myeloproliferative neoplasm.

Design and Methods

The details of the study population have been described previously.[4] We identified all incident patients diagnosed from 1958 to 2005 with a myeloproliferative neoplasm from the nationwide Swedish Cancer Registry. In addition, we retrieved information on incident MPN patients through our national MPN network.

For each MPN patient, four population-based controls matched by sex, year of birth, and county were chosen randomly from the Swedish Population database. All controls had to be alive at the time of myeloproliferative neoplasm diagnosis for the corresponding case and free of hematologic malignancy at the date of the corresponding case's diagnosis.

Information on occurrence and date of autoimmune disease was obtained from the Inpatient Registry.

Using logistic regression models adjusted for age, sex, calendar period, and region, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) as measures of relative risks. To limit the influence of detection bias, we excluded autoimmune disease diagnosed less than one year prior to diagnosis of myeloproliferative neoplasm.

Results and Discussion

A total of 11,039 (6217 PV, 2838 ET, 1172 PMF, and 812 MPN not otherwise specified (NOS)) MPN patients diagnosed in Sweden in 1958-2005 together with 43,550 population-based matched controls were included in our study (Table 1).

A total of 288 (2.6%) MPN patients had a previous personal history of autoimmunity. A prior history of any autoimmune disease was associated with an increased risk of MPNs (OR=1.2; 95% CI 1.0-1.3; *P*=0.021; Table 2). Furthermore, there was an increased risk associated with autoimmune diseases without detectable antibodies (1.6; 1.3-2.0; Table 2). Specifically, we found an increased risk of myeloproliferative neoplasms associated with a prior history of immune thrombocytopenic purpura (ITP) (2.9; 1.7-7.2), Crohn's disease (1.8; 1.1-3.0), polymyalgia rheumatica (PMR) (1.7; 1.2-2.5), giant cell arteritis (5.9; 2.4-14.4), Reiter's syndrome (15.9; 1.8-142) and aplastic anemia (7.8; 3.7-16.7). In analyses stratified by MPN subgroup, age at diagnosis, and sex, based on small numbers, the results were virtually unchanged (Table 2).

In the most comprehensive investigation to date, we assessed a broad range of autoimmune diseases in relation to specific myeloproliferative neoplasms. We found that individuals with a prior history of any autoimmune disease had a 20% increased risk of developing a myeloproliferative neoplasm. When we evaluated individual autoimmune diseases, we found a 2- to 3-fold elevated risk for myeloproliferative neoplasms among patients with a history of immune thrombocytopenic purpura, Crohn's disease, and polymyalgia rheumatica. The most prominent risks were found among persons with a history of giant cell arteritis, aplastic anemia, and Reiter's syndrome. Our findings are consistent with what is to our knowledge the only prior study based on the US

Table 1. Characteristics of myeloproliferative neoplasm patients and controls.

Variable	MPN patients					Controls
	PV	ET	PMF	MPN NOS	Any MPN	
N. (%) of patients	6,217 (100)	2,838 (100)	1,172 (100)	812 (100)	11,039 (100)	43,550 (100)
Male, sex, n (%)	3,078 (49.5)	1,214 (42.8)	644 (55.0)	401 (49.4)	5,337 (48.4)	21,152 (48.6)
Age at diagnosis, y [mean (range)]	66 (3-97)	66 (1-98)	69 (16-93)	71 (20-97)	67 (1-90)	67 (1-98)
Age group at diagnosis, n. (%)						
Younger than 40 years	208 (3.4)	212 (7.5)	22 (1.9)	18 (2.2)	460 (4.2)	1,840 (4.2)
40-49 years	443 (7.1)	253 (8.9)	57 (4.9)	41 (5.1)	794 (7.2)	3,174 (7.3)
50-59 years	1,037 (16.7)	385 (13.6)	150 (12.8)	74 (9.1)	1,646 (14.9)	6,572 (15.0)
60-69 years	1,661 (26.7)	580 (20.4)	310 (26.4)	177 (21.8)	2,728 (24.7)	10,826 (24.9)
70-79 years	1,968 (31.6)	865 (30.5)	431 (36.8)	269 (33.1)	3,533 (32.0)	13,834 (31.8)
Older than 80 years	900 (14.5)	543 (19.1)	202 (17.2)	233 (28.7)	1,878 (17.1)	7,304 (16.8)
Calendar year of diagnosis, n. (%)						
1958-1965	590 (9.5)	48 (1.7)	1 (0.1)	—	639 (5.8)	2,556 (5.9)
1966-1975	1,172 (18.9)	145 (5.1)	124 (10.6)	—	1,441 (13.1)	5,747 (13.2)
1976-1985	1,364 (21.9)	201 (7.1)	328 (28.0)	—	1,893 (17.2)	7,443 (17.1)
1986-1995	1,527 (25.5)	1,542 (54.3)	412 (35.2)	159 (19.6)	3,640 (32.9)	14,250 (32.7)
1996-2005	1,564 (25.2)	902 (31.8)	307 (26.2)	653 (80.4)	3,426 (31.0)	13,554 (31.1)
Data source, n. (%)						
Cancer Registry	5,491 (88.3)	2,367 (83.4)	1,030 (87.9)	812 (100)	3,998 (87.9)	38,260 (87.8)
Hospital--based Registries	726 (11.7)	471 (16.6)	142 (12.1)	—	1,339 (12.1)	5,290 (12.2)

MPN indicates myeloproliferative neoplasm; PV, polycythemia vera; ET, essential thrombocythemia; PMF, myelofibrosis; and NOS, not otherwise specified.

Table 2. Risk of developing myeloproliferative neoplasms following a personal history of autoimmunity.

Category/ condition	MPN patients (n=11,0039)	Controls (n=43,550)	OR* (95% CI)	PV (n=6,217)	Ctrl (n=24,565)	OR* (95% CI)	ET (n=2,838)	N. Ctrl (n=10,788)	OR* (95% CI)	PMF (n=1,172)	Ctrl (n=4,606)	OR* (95% CI)	MPN NOS (n=812)	Ctrl (n=3,199)	OR* (95% CI)
Any autoimmune disease**	288	972	1.2 (1.0-1.3)	117	471	1.0 (0.8-1.2)	87	281	1.2 (1.0-1.6)	41	122	1.3 (0.9-1.9)	43	98	1.8 (1.2-2.6)
Autoantibodies detectable	179	709	1.0 (0.8-1.2)	72	346	0.8 (0.6-1.1)	52	200	1.0 (0.7-1.4)	24	89	1.1 (0.7-1.7)	31	74	1.7 (1.1-2.6)
Systemic involvement	92	368	1.0 (0.8-1.2)												
Rheumatoid arthritis	84	320	1.0 (0.8-1.3)	31	153	0.8 (0.5-1.2)	30	88	1.3 (0.9-2.0)	10	45	0.9 (0.4-1.7)	13	34	1.5 (0.5-2.9)
Systemic sclerosis	3	20	0.6 (0.2-2.0)												
Sjögren's syndrome	4	22	0.7 (0.2-2.1)												
Systemic lupus erythematosus	7	21	1.3 (0.6-3.1)												
Organ involvement	77	315	1.0 (0.7-1.2)	32	154	0.8 (0.6-1.2)	17	92	0.7 (0.4-1.2)	12	37	1.3 (0.7-2.5)	16	32	2.0 (1.1-3.6)
Pernicious anemia	21	96	0.9 (0.5-1.4)	12	37	1.3 (0.7-2.5)	1	35	0.1 (0.0-0.8)	2	15	0.5 (0.1-2.3)	6	9	2.6 (0.9-7.4)
Graves' disease	4	38	0.4 (0.1-1.2)												
Guillian Barré syndrome	3	15	0.8 (0.2-2.7)												
Chronic rheumatic heart disease	22	84	1.0 (0.6-1.6)	10	50	0.8 (0.4-1.6)	5	22	0.9 (0.3-2.3)	4	6	2.6 (0.7-9.4)	3	6	2.0 (0.5-7.9)
Multiple sclerosis	13	46	1.1 (0.6-2.1)	6	25	1.0 (0.4-2.3)	3	13	0.9 (0.3-3.2)	1	2	2.0 (0.2-21.9)	3	6	2.0 (0.5-7.9)
Addison's disease	4	10	1.6 (0.5-5.0)												
ITP	8	11	2.9 (1.2-7.2)	2	6	1.3 (0.3-6.5)	3	4	3.0 (0.7-13.2)	3	0	Inf	0	1	0
Males	5	4	5.0 (1.3-18.5)												
Females	3	7	1.7 (0.4-6.5)												
Age <67 yrs.	3	3	4.0 (0.8-19.8)												
Age >67 yrs.	5	8	2.4 (0.8-7.5)												
Latency >5 yrs.	4	7	2.3 (0.7-7.7)												
Myasthenia gravis	3	9	1.3 (0.4-4.9)												
Autoantibodies not detectable	116	291	1.6 (1.3-2.0)	46	140	1.3 (0.9-1.8)	40	90	1.8 (1.2-2.6)	17	33	2.11 (1.1-3.7)	3	28	1.8 (0.9-3.6)
Rheumatic fever	5	27	0.7 (0.3-1.9)	3	13	0.9 (0.3-3.2)	2	11	0.7 (0.2-3.2)	0	3	0	0	0	NA
Sarcoidosis	10	51	0.8 (0.4-1.5)	3	24	0.5 (0.2-1.6)	6	17	1.4 (0.6-3.5)	1	5	0.8 (0.1-6.8)	0	5	0
Crohn`s disease	22	48	1.8 (1.1-3.0)	6	22	1.1 (0.4-2.7)	9	11	3.3 (1.3-7.9)	1	8	0.5 (0.1-4.0)	6	7	3.4 (1.1-10.1)
Males			1.4 (0.6-3.1)												
Females			2.2 (1.2-4.3)												
Age < 67 years			2.3 (1.2-4.5)												
Age > 67 years			1.3 (0.6-2.9)												
Latency >5 years			1.8 (1.0-3.2)												
Ulcerative colitis	23	70	1.3 (0.8-2.1)	14	34	1.6 (0.9-3.1)	7	18	1.6 (0.6-3.7)	1	13	0.3 (0.0-2.3)	1	5	0.8 (0.1-6.8)

to be continued on the next page.

Table 2. Risk of developing myeloproliferative neoplasms following a personal history of autoimmunity. *(continued from previous page)*

Category/ condition	MPN patients (n=11,0039)	Controls (n=43,550)	OR* (95% CI)	PV (n=6,217)	Ctrl (n=24,565)	OR* (95% CI)	ET (n=2,838)	Ctrl (n=10,788)	OR* (95% CI)	PMF (n=1,172)	Ctrl (n=4,606)	OR* (95% CI)	MPN NOS (n=812)	Ctrl (n=3,199)	OR* (95% CI)
Polymyalgia rheumatica	46	104	1.7 (1.2-2.5)	17	39	1.7 (1.0-3.0)	18	30	2.3 (1.3-4.2)	6	9	2.6 (0.9-7.4)	5	26	0.7 (0.3-2.0)
Males			1.8 (1.0-3.2)												
Females			1.7 (1.1-2.6)												
Age < 67 years			3.3 (1.0-10.9)												
Age > 67 years			1.6 (1.1-2.4)												
Latency >5 years			2.2 (1.4-3.6)												
Ankylosing spondylitis	10	35	1.1 (0.6-2.3)	4	23	0.7 (0.2-2.0)	5	7	2.8 (0.9-9.0)	1	3	1.3 (0.1-12.7)	0	2	Inf
Psoriasis	22	88	1.0 (0.6-1.6)	7	43	0.6 (0.3-1.4)	9	29	1.2 (0.6-2.6)	5	6	3.3 (1.0-10.8)	1	10	0.4 (0.1-3.1)
Giant cell arteritis	12	8	5.9 (2.4-14.4)	4	4	3.9 (1.0-15.8)	4	2	7.8 (1.4-42.4)	1	1	3.9 (0.2-63.1)	3	1	11.8 (1.2-113.7)
Males			7.9 (2.0-31.5)												
Females			4.7 (1.4-15.3)												
Age < 67 years			Inf												
Age > 67 years			4.9 (1.9-12.4)												
Latency >5 years			2.4 (0.6-9.9)												
Reiter's syndrome	4	1	15.9 (1.8-142.0)												
Aplastic anemia	20	10	7.8 (3.7-16.7)	6	4	5.9 (1.7-21.0)	3	4	2.9 (0.7-13.1)	8	1	31.7 (4.0-253.6)	3	1	11.8 (1.2-113.8)
Males			8.1 (5.4-12.2)												
Females			4.8 (3.9-6.9)												
Age < 67 years			6.6 (4.3-10.3)												
Age > 67 years			5.8 (4.1-8.0)												
Latency >5 years			7.8 (1.4-42.8)												

**ORs are adjusted for categorical year of birth, date of diagnosis, sex, and county. **Overall categories total to less than the sum of the individual categories because some individuals have more than one AI. ***NA: Not applicable. ****Inf: Infinity. Only conditions with more than 2 cases are presented.*

Surveillance Epidemiology and End Results (SEER)-Medicare database, that included 1,017 myeloproliferative neoplasm cases diagnosed in 2000 or 2001, at the age of 66 years or older.[15] A major limitation in that study was the lack of information on MPN subtypes and that the MPN cohort included a variety of other conditions, such as mastocytosis.[15]

Our findings may be important for several reasons. Potentially, one might conjecture that the underlying explanation for our findings is the fact that autoimmune conditions cause immune-related or inflammation driven tumorigenesis leading to myeloproliferative neoplasms. Alternatively, the treatments given to patients with autoimmune disease (steroids, anti-inflammatory and immunosuppressive agents) might play a role in the risk of myeloproliferative neoplasms. Also, there might be shared common genetic and/or environmental susceptibility in autoimmune diseases and myeloproliferative neoplasms. The observation of an increased risk of myeloproliferative neoplasms following Crohn's disease, but not ulcerative colitis, is particularly intriguing. Crohn's disease is an inflammatory bowel disease, with a well established risk of developing colorectal cancer.[17] Associations with other malignancies have been reported.[18] Interestingly, a recent genome-wide association study in patients with Crohn's disease found evidence of an association in the region containing JAK2.[19] We found prior history of polymyalgia rheumatica and giant cell arteritis to be associated with an increased risk of myeloproliferative neoplasms. It has been suggested that the prevalence of cancer is increased in patients with giant cell arteritis, however this is controversial.[20,21] Polymyalgia rheumatica and giant cell arteritis can mimick other conditions, with features such as thrombocytosis and leukocytosis, with patients being misclassified as myeloproliferative neoplasms.[22,23] However, in our latency analyses on polymyalgia rheumatica we found the risk estimate to be significantly elevated more than five years prior to myeloproliferative neoplasms. Furthermore, aplastic anemia, characterized by pancytopenia and reduced marrow cellularity, is treated with immunosuppressive therapy and/or stem cell transplantation. It is associated with an increased risk for myelodysplastic syndrome, leukemias and some solid tumors.[24-26] It has not been previously associated with risk of myeloproliferative neoplasms.

The strengths of our study include its large size and high-quality data from Sweden in a stable population with access to standardized universal medical health care during the study period. Furthermore, the use of the nationwide register-based case-control design ruled out recall-bias and ensured a population-based setting and the possibility to come to generalized conclusions from our findings.

Limitations include lack of clinical data, lack of information on potential confounders (although the design ensured adjustment for sex, age, and geographical location), absence of a systematic blinded validation of all myeloproliferative neoplasm diagnoses, and a large num-

ber of tested variables. Furthermore, the use of inpatient data led to under-ascertainment of less severe forms of autoimmune diseases and our findings may apply mainly to severe forms of autoimmunity. However, because personal history of autoimmune diseases was assessed similarly among the patients with myeloproliferative neoplasms and controls, any under-diagnosis should be non-differential, and any bias should be toward the null.

In conclusion, the research field in myeloproliferative neoplasms is rapidly evolving, and progress is being made in understanding the pathogenesis of these diseases. Based on over 11,000 MPN patients, we found individuals with a personal history of autoimmunity to have a 20% increased risk of developing a myeloproliferative neoplasm. Certain autoimmune conditions, including giant cell arteritis, aplastic anemia, and Reiter's syndrome were associated with highly elevated risks. Future studies are needed to uncover underlying mechanisms of our novel findings.

Authorship and Disclosures

SYK, MB, LRG and OL, designed the study; SYK, MB, and OL obtained data and initiated this work; LRG performed all statistical analyses. All the authors were involved in the interpretation of the results; SYK and OL wrote the report. All authors read, gave comments, and approved the final version of the manuscript. All the authors had full access to the data in the study and take responsibility for the accuracy of the data analysis.

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