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ORIGINAL REPORT

Chronic Immune Stimulation Might Act As a Trigger for the Development of Acute Myeloid Leukemia or Myelodysplastic Syndromes

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ABSTRACT

Purpose
Patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) often present with infections, but there are little data to assess whether a personal history of selected infections may act as pathogenic triggers. To additionally expand our knowledge on the role of immune stimulation in the causation of AML and MDS, we have conducted a large, population-based study to evaluate the risk of AML and MDS associated with a prior history of a broad range of infections or autoimmune diseases.

Patients and Methods
By using population-based central registries in Sweden, we included 9,219 patients with AML, 1,662 patients with MDS, and 42,878 matched controls. We used logistic regression to calculate odds ratios (ORs) and 95% CIs for the association of AML or MDS with infectious and/or autoimmune diseases.

Results
Overall, a history of any infectious disease was associated with a significantly increased risk of both AML (OR, 1.3; 95% CI, 1.2 to 1.4) and MDS (OR, 1.3; 95% CI, 1.1 to 1.5). These associations were significant even when we limited infections to those occurring 3 or more years before AML/MDS. A previous history of any autoimmune disease was associated with a 1.7-fold (95% CI, 1.5 to 1.9) increased risk for AML and 2.1-fold (95% CI, 1.7 to 2.6) increased risk for MDS. A large range of conditions were each significantly associated with AML and MDS.

Conclusion
Our novel findings indicate that chronic immune stimulation acts as a trigger for AML/MDS development. The underlying mechanisms may also be due to a common genetic predisposition or an effect of treatment for infections/autoimmune conditions.

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INTRODUCTION

Acute myeloid leukemia (AML) remains a highly fatal malignancy, with approximately 10% to 15% 5-year survival in patients age 60 years and older.[1,2] Myelodysplastic syndrome (MDS) includes a range of hematologic conditions united by ineffective hematopoiesis and an increased risk of transformation to AML.[3]

Prior case reports and smaller studies suggest that ionizing radiation and certain chemicals (eg, benzene) may play important roles in the development of AML and MDS.[4-6] Also, patients treated with chemotherapy as a result of other malignancies have a higher risk of MDS and AML.[1,7,8] Furthermore, patients with certain diseases/syndromes (eg, myeloproliferative neoplasms [MPNs] and Down syndrome) have a propensity to develop AML and MDS.[9-11] However, the majority of patients with AML/MDS have no history of any known risk factor.

Despite the severe infections in patients with AML at presentation, there are little data to assess whether preceding infections may play a plausible role in the causation of AML. In one study that included 624 patients with AML, a weak association with common childhood viral disease was found, but no other immune-related condition was associated.[12] Furthermore, in a study with results that were based on 236 patients, a significantly increased risk for AML was observed in patients with previous tuberculosis, whereas various other types of infections and chronic conditions were not associated with an excess risk.[13]

To increase our understanding on the role of immune-related, infectious, and inflammatory conditions in the development of AML and MDS, we conducted a large, population-based, case-control study by use of linked registry data from Sweden that included 9,219 patients with AML, 1,662 patients with MDS, and 42,878 population-based controls. We evaluated the association between a prior personal history of infections and a broad range of autoimmune diseases and the development of AML and MDS.

PATIENTS AND METHODS

Registries, Patients, and Control Participants

Details of the study populations have been described previously.[2,14] In brief, Sweden provides universal medical health care for the entire population, which is currently just over 9 million people. Patients with AML and MDS in Sweden are typically diagnosed, treated, and observed clinically by physicians at hospital-based hematology units.

Since 1958, all physicians, pathologists, and cytologists in Sweden are obliged by law to report each occurrences of cancer that they diagnose or treat to the centralized, nationwide Swedish Cancer Registry.[15] In a recent validation study, we found the overall completeness and diagnostic accuracy of the Registry to be greater than 90%.[16] From the Cancer Registry, we identified all patients with AML who were diagnosed from January 1, 1965, through December 31, 2004, and all patients with MDS who were diagnosed from January 1, 1993, through December 31, 2004. To minimize risk for bias in this study, we excluded patients with another cancer diagnosed before their AML or MDS diagnoses.

For each patient with AML and MDS, four population-based control participants (matched by sex, year of birth, and county of residence) were chosen randomly from the Swedish Population database. All control participants had to be alive at the time of AML/MDS diagnosis for the corresponding case patient and had to be without a hematologic malignancy diagnosed before the date of AML/MDS diagnosis for their corresponding case patient.

Information on occurrence and date of infections and autoimmune diseases was obtained from the Inpatient Registry (established in 1964). The seventh, eighth, ninth, and tenth revisions of the International Classification of Diseases were used to code diagnoses of specific infectious and autoimmune diseases. Conditions included in the analyses were in accord with previously published studies.[17-19] The condition did not have to be that for which the patient was admitted, it only had to be in the list for a hospitalization episode. In accord with previous studies,[20] autoimmune conditions were categorized according to those that generally have detectable autoantibodies and those that do not. Here, we present results for individual immune stimulatory conditions only if three or more people with the condition developed AML or MDS.

Statistical Analysis

We used logistic regression to calculate odds ratios (ORs) and 95% CIs for the association of AML or MDS with infectious and/or autoimmune diseases by adjusting for year of birth (categorized into quartiles), year of patient diagnosis (categorized into quartiles), and sex. To avoid detection bias, we excluded the first year before AML/MDS diagnosis from the analyses. To evaluate the possibility that undetected AML/MDS could cause immune-related and/or infectious conditions (ie, reverse causality), we also analyzed infectious and autoimmune conditions that were diagnosed at least 3 years before AML/MDS. The occurrence of multiple different infectious or autoimmune disease diagnoses in the same individual were each counted in the analyses, but we assessed the possible differential effect as a result of multiple diagnoses occurring in the same individual. We analyzed the case-control difference in the occurrence of multiple conditions and conducted sensitivity analyses by removing patients and controls with multiple conditions from the analysis. Stratified analyses that were based on AML and MDS subtype were not performed because of the small numbers in each category. We also stratified results on the basis of age of diagnosis of AML and looked at patients diagnosed when younger than age 65 years and younger than age 40 years. When discussing significance levels, we refer to nominal *P* values.

Table 1. Characteristics of Patients With AML and MDS and Matched Control Participants

Variable	AML Patients (n = 9,219) No.	AML Patients (n = 9,219) %	AML Controls (n = 36,389)	MDS Patients (n = 1,662) No.	MDS Patients (n = 1,662) %	MDS Controls (n = 6,489)
Median age at diagnosis, years	68			76		
% male	52.8		53.0	54.9		54.9
Age group, years						
< 40	1,262	13.7		33	2.0	
40-49	704	7.6		30	1.8	
50-59	1,057	11.5		102	6.1	
60-69	1,978	21.5		266	16.0	
70-79	2,609	28.3		639	38.5	
≥ 80	1,609	17.4		592	35.6	
Year of diagnosis						
Before 1990	5,257	57.0		0		
1990-1994	1,487	16.1		250	15.0	
1995-2000	1,236	13.4		719	43.3	
After 2000	1,239	13.5		693	41.7	

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

RESULTS

A total of 9,219 patients with primary AML and 1,662 patients with primary MDS, as well as the 36,389 and 6,489 population-based controls, respectively, were included in the study. As listed in Table 1, 52.8% of the patients with AML and 54.9% of the patients with MDS were men, and the median ages at diagnoses were 68 years and 76 years for AML and MDS, respectively.

Infections and Risk of AML and MDS

Overall, a history of any infectious disease was associated with a 1.3-fold significantly increased risk of AML (Table 2). A broad range of infections were significantly associated with risk of AML, including pneumonia, tuberculosis, intestinal infections, septicemia, hepatitis C, pyelonephritis, sinusitis, nasopharyngitis, upper respiratory tract infection, meningitis, cytomegalovirus infection, and cellulitis. In latency analyses (ie, of infections 3 or more years before AML), many of these infections remained significantly associated with AML.

The results for MDS are listed in Table 3. As with AML, a history of any infection was associated with a 1.3-fold significantly increased risk of MDS and remained significant in the 3-year latency analysis. However, fewer individual subgroups of infections were associated with MDS. We analyzed primary AML occurrences that were diagnosed in patients younger than age 65 years and younger than age 40 years, and we found that the overall patterns of increased risks as a result of any infection were similar in these younger age groups (data not shown).

Autoimmune Disease and Risk of AML and MDS

Associations between an autoimmune disease and AML are listed in Table 4. A total of 359 patients had a history of any autoimmune

Table 2. Personal History of Infections and Risk of AML

Category or Condition	Participants				Latency More Than 3 Years Before AML Diagnosis			
	No. of AML Occurrences (n = 9,468)	No. of Controls (n = 37,384)	OR	CI	No. of AML Occurrences	No. of Controls	OR	CI
Any infection	749	2,309	1.3	1.2 to 1.4	565	1,846	1.2	1.1 to 1.3
Pneumonia	251	768	1.3	1.1 to 1.5	185	560	1.3	1.1 to 1.5
Tuberculosis	59	132	1.8	1.2 to 2.4	41	111	1.5	1.0 to 2.1
Influenza	29	90	1.3	0.8 to 1.9	24	74	1.3	0.8 to 2.0
Intestinal infection	120	384	1.2	1.0 to 1.5	88	308	1.1	0.9 to 1.4
Septicemia	45	114	1.6	1.1 to 2.2	17	82	0.8	0.5 to 1.4
Herpes simplex	7	18	1.5	0.6 to 3.7	5	16	1.2	0.5 to 3.4
Herpes zoster	24	85	1.1	0.7 to 1.7	20	63	1.2	0.8 to 2.1
Hepatitis C	7	7	4.0	1.4 to 11.4	7	7	4.0	1.4 to 11.4
Infectious mononucleosis	3	12	1.0	0.3 to 3.5	2	11	0.7	0.2 to 3.3
Pyelonephritis	66	163	1.6	1.2 to 2.1	48	131	1.4	1.0 to 2.0
Cystitis	78	291	1.1	0.8 to 1.4	54	203	1.0	0.8 to 1.4
Gonorrhea	4	20	0.8	0.3 to 2.3	3	20	0.6	0.2 to 2.0
Syphilis	4	15	1.1	0.4 to 3.2	3	12	1.0	0.3 to 3.5
Sinusitis	33	68	1.9	1.3 to 2.9	26	58	1.8	1.1 to 2.8
Otitis media	42	173	1.0	0.7 to 1.4	30	151	0.8	0.5 to 1.2
Nasopharyngitis	38	98	1.5	1.1 to 2.2	31	87	1.4	0.9 to 2.1
Upper respiratory tract infection	116	352	1.3	1.1 to 1.6	90	308	1.2	0.9 to 1.5
Encephalitis	3	19	0.6	0.2 to 2.1	3	14	0.9	0.3 to 3.0
Meningitis	13	26	2.0	1.0 to 3.9	9	22	1.6	0.8 to 3.5
Lyme disease	4	48	0.3	0.1 to 0.9	4	48	0.3	0.1 to 0.9
Myocarditis	5	25	0.8	0.3 to 2.1	5	22	0.9	0.3 to 2.4
Osteomyelitis	13	43	1.2	0.6 to 2.2	10	36	1.1	0.5 to 2.2
Cytomegalovirus	7	5	5.6	1.8 to 17.5	6	3	7.9	2.0 to 31.6
Tonsillitis	23	74	1.2	0.8 to 2.0	17	61	1.1	0.6 to 1.9
Cellulitis	99	249	1.6	1.2 to 2.0	62	197	1.2	0.9 to 1.7
Empyema	3	9	1.3	0.4 to 4.9	2	8	1.0	0.2 to 4.6

NOTE. ORs were adjusted for categoric 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 autoimmune disease.
Abbreviations: AML, acute myeloid leukemia; OR, odds ratio.

disease before their AML diagnoses, and the risk of AML for total autoimmune disease was 1.7-fold significantly increased. Furthermore, a significantly increased risk of AML was observed among patients with a history of each of the three categories of autoimmune diseases tested, including systemic, any autoimmune disease with organ involvement, and autoimmune disease without detectable antibodies. A broad range of conditions were each significantly associated with a later diagnosis of AML, including rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, pernicious anemia, autoimmune hemolytic anemia, immune thrombocytopenic purpura, polyarteritis nodosa, Wegener's granulomatosis, polymyalgia rheumatica, giant cell arteritis, aplastic anemia, and psoriasis. When we evaluated risk for AML by latency (time between autoimmune disease and AML), the increased AML risk remained statistically significant at more than 3 years of latency among patients with all the three categories—any previous autoimmune disease, any autoimmune disease with organ involvement, any autoimmune disease without detectable autoantibodies—as well as many of the individual conditions (Table 4).

The results for MDS were similar to those for AML despite the smaller number of patients (Table 5). Overall, a history of any autoimmune disease was associated with a two-fold significantly increased risk of MDS. In addition, each of the large categories of autoimmune diseases was significantly associated with subsequent MDS as well as many of the individual conditions. As with AML, many of the significant associations remained significant even after limiting the comparison to those who had autoimmune diseases 3 or more years before MDS.

We also analyzed primary AML occurrences in patients diagnosed when younger than age 65 years and younger than age 40 years and found that the overall patterns of increased risk as a result of the broad categories of autoimmune diseases were similar in these younger age groups (data not shown).

Multiple Infections and Autoimmune Conditions

We compared the distribution of numbers of different infections and autoimmune conditions in patients and controls. For infections, there were slightly more patients than controls that had three or more different infections with borderline significance ($P = .052$). In the case of autoimmune diseases, there were slightly more patients with multiple conditions than controls, but the difference was not significant (not shown). If we eliminated patients and controls with the highest number of conditions, the results changed little (data not shown). Finally, in a logistic model allowing for the variable of any autoimmune condition and the variable of any infection, both the variable of any infection (OR, 1.3; 95% CI, 1.2 to 1.4) and the variable of any

Table 3. Personal History of Infections and Risk of MDS

Category or Condition	Participants				Latency 3 Years Before MDS Diagnosis			
	No. of MDS Occurrences (n = 1,662)	No. of Controls (n = 6,489)	OR	CI	No. of Occurrences	No. of Controls	OR	CI
Any infection	224	684	1.3	1.1 to 1.5	182	536	1.4	1.1 to 1.6
Pneumonia	85	255	1.3	1.0 to 1.7	61	188	1.3	1.0 to 1.7
Tuberculosis	10	35	1.1	0.6 to 2.3	10	31	1.3	0.6 to 2.6
Influenza	9	33	1.1	0.5 to 2.2	7	25	1.1	0.5 to 2.5
Intestinal infection	35	110	1.2	0.9 to 1.8	29	91	1.2	0.8 to 1.9
Septicemia	13	46	1.1	0.6 to 2.1	7	28	1.0	0.4 to 2.2
Herpes simplex	4	5	3.1	0.8 to 11.6	3	4	2.9	0.7 to 13.1
Herpes zoster	12	30	1.6	0.8 to 3.1	11	20	2.1	1.0 to 4.5
Pyelonephritis	25	66	1.5	0.9 to 2.4	18	52	1.4	0.8 to 2.3
Cystitis	30	97	1.2	0.8 to 1.8	22	62	1.4	0.9 to 2.3
Sinusitis	5	18	1.1	0.4 to 2.9	3	13	0.9	0.3 to 3.2
Otitis media	13	37	1.4	0.7 to 2.6	12	33	1.4	0.7 to 2.8
Nasopharyngitis	6	20	1.2	0.5 to 2.9	3	16	0.7	0.2 to 2.5
Upper respiratory tract infection	25	84	1.2	0.8 to 1.8	19	69	1.1	0.7 to 1.8
Encephalitis	3	5	2.4	0.6 to 10.0	3	4	3.0	0.7 to 13.3
Meningitis	4	4	3.9	1.0 to 15.7	4	4	3.9	1.0 to 15.7
Osteomyelitis	7	13	2.1	0.8 to 5.3	7	12	2.3	0.9 to 5.8
Cellulitis	37	87	1.7	1.1 to 2.5	29	69	1.7	1.1 to 2.6
Empyema	3	4	2.9	0.7 to 13.1	3	3	3.9	0.8 to 19.4

NOTE. ORs were adjusted for categoric 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 autoimmune disease.
Abbreviations: MDS, myelodysplastic syndrome; OR, odds ratio.

autoimmune condition (OR, 1.6; 95% CI, 1.4 to 1.8) were highly significant, which indicates that these are independent risk factors that contribute to the risk of AML.

DISCUSSION

For the first time to our knowledge, in a population-based setting with a sample of more than 9,000 patients with primary AML, more than 1,500 patients with primary MDS, and approximately 43,000 matched controls, we found a personal history of any infection as well as a broad range of specific infections to increase the risk of both AML and MDS. Specifically, AML was associated with prior pneumonia, tuberculosis, intestinal infections, septicemia, hepatitis C, pyelonephritis, sinusitis, nasopharyngitis, upper respiratory tract infection, meningitis, cytomegalovirus infection, and cellulitis. MDS was increased among patients with previous pneumonia and cellulitis. There are little data in the literature on the role of infections in the etiology of AML.[12,13] In review articles, the general conclusion is that there is either no association or that there are insufficient data.[21,22] The mechanisms for an increased risk for AML and MDS among patients with a previous infection are not clear but may involve an underlying immune dysfunction that could also predispose to AML/MDS. Alternatively, infections/host responses could induce early leukemogeneic events. These novel findings need to be verified in other studies, for example in large cohorts of patients with chronic immune stimulation disease. However, we and others have reported similar findings in certain lymphoid malignancies.[23,24]

We also found a significantly increased risk of AML and MDS associated with a prior history of autoimmune disease. We found that a personal history of rheumatoid arthritis, autoimmune hemolytic anemia, immune thrombocytopenic purpura, Wegener's granulomatosis, polymyalgia rheumatica, giant cell arteritis, psoriasis, and aplastic anemia increased the risk of both AML and MDS. The risk for AML increased by 70% in patients who had any autoimmune disease. The highest risks were observed in patients with prior Wegener's granulomatosis, autoimmune hemolytic anemia, polyarteritis nodosa, giant cell arteritis, and aplastic anemia; however, for some of these conditions, the numbers of patients were small. In MDS, the risk increased two-fold in patients with any autoimmune disease. Many of our findings are consistent with a study that was based on the US Surveillance, Epidemiology, and End Results (SEER) –Medicare database, which included patients with primary and secondary AML and MDS age 67 years or older.[25] The associations that we observed with immune thrombocytopenic purpura, Wegener's granulomatosis, psoriasis, giant cell arteritis, and aplastic anemia have not been previously reported. Some of these conditions have not been previously associated with an increased risk of cancer. We recently showed, in a study that included 11,039 patients with MPN, that a previous autoimmune disease was associated with a 20% increased risk of MPN. Specifically, there was a significantly increased risk in patients with prior immune thrombocytopenic purpura, Crohn's disease, polymyalgia rheumatica, giant cell arteritis, Reiter's syndrome, and aplastic anemia.[14] This suggests that some of these conditions cause susceptibility to multiple myeloid malignancies. In addition, aplastic anemia is associated with an increased risk for MDS, leukemias, and some solid tumors.[26] Also consistent with our results, an increased risk of AML after immune thrombocytopenic purpura and autoimmune hemolytic anemia,[27] as well as after rheumatoid arthritis diagnosis, was found in two Swedish studies.[28] Consistent with the SEER study,[25] we found that rheumatoid arthritis was associated with an increased risk

Table 4. Personal History of Autoimmune Disease and Risk of AML

Category or Condition	Participants				Latency More Than 3 Years Before AML Diagnosis			
	No. of AML Occurrences (n = 9,468)	No. of Controls (n = 37,384)	OR	CI	No. of AML Occurrences	No. of Controls	OR	CI
Total autoimmune disease	359	861	1.7	1.5 to 1.9	251	691	1.4	1.3 to 1.7
Systemic involvement	116	320	1.4	1.2 to 1.8	82	269	1.2	0.9 to 1.5
Rheumatoid arthritis	102	292	1.4	1.1 to 1.7	70	241	1.1	0.9 to 1.5
Systemic lupus erythematosus	11	20	2.2	1.0 to 4.5	10	19	2.1	1.0 to 4.5
Systemic sclerosis	6	12	2.0	0.7 to 5.2	4	10	1.6	0.5 to 5.0
Sjögren's syndrome	5	10	2.0	0.7 to 5.7	4	10	1.6	0.5 to 5.0
Organ involvement	116	301	1.5	1.2 to 1.9	85	233	1.4	1.1 to 1.9
Hashimoto's thyroiditis	6	6	3.9	1.3 to 12.1	6	6	3.9	1.3 to 12.1
Graves' disease	5	37	0.5	0.2 to 1.4	4	30	0.5	0.2 to 1.5
Addison's disease	4	13	1.2	0.4 to 3.7	2	9	0.9	0.2 to 4.0
Pernicious anemia	29	74	1.5	1.0 to 2.4	18	53	1.3	0.8 to 2.3
Autoimmune hemolytic anemia	11	3	14.4	4.0 to 51.5	9	3	11.7	3.2 to 43.3
Immune thrombocytopenic purpura	7	7	4.0	1.4 to 11.3	4	5	3.2	0.9 to 11.8
Primary biliary cirrhosis	3	13	0.9	0.3 to 3.2	2	11	0.7	0.2 to 3.2
Polyarteritis nodosa	4	1	15.7	1.8 to 140.4	4	1	15.7	1.8 to 140.4
Diabetes type I	5	11	1.8	0.6 to 5.2	5	9	2.2	0.8 to 6.7
Wegener's granulomatosis	6	1	23.8	2.9 to 197.5	6	1	23.8	2.9 to 197.5
Chronic rheumatic heart disease	20	71	1.1	0.7 to 1.8	12	58	0.8	0.4 to 1.5
Multiple sclerosis	8	30	1.1	0.5 to 2.3	7	27	1.0	0.5 to 2.3
Autoantibodies not detectable	161	293	2.2	1.8 to 2.7	107	230	1.9	1.5 to 2.3
Rheumatic fever	7	11	2.5	1.0 to 6.5	5	9	2.2	0.7 to 6.6
Sarcoidosis	18	42	1.7	1.0 to 2.9	12	36	1.3	0.7 to 2.5
Crohn's disease	11	44	1.0	0.5 to 1.9	7	33	0.8	0.4 to 1.9
Ulcerative colitis	11	56	0.8	0.4 to 1.5	9	45	0.8	0.4 to 1.6
Ankylosing spondylitis	8	18	1.8	0.8 to 4.1	8	14	2.3	1.0 to 5.4
Polymyalgia rheumatic	55	54	4.0	2.8 to 5.9	36	36	3.9	2.5 to 6.3
Psoriasis	27	64	1.7	1.1 to 2.6	21	57	1.5	0.9 to 2.4
Giant cell arteritis	15	6	9.8	3.8 to 25.3	9	2	17.6	3.8 to 81.6
Aplastic anemia	22	9	9.7	4.5 to 21.0	6	5	4.8	1.5 to 15.6

NOTE. ORs were adjusted for categoric year of birth, date of diagnosis, sex, and county. When presented in square brackets, two-sided *P* values that were based on Fisher's exact test were given when no patient or control had the specified condition. Overall categories total to less than the sum of the individual categories because some individuals have more than one autoimmune disease.

Abbreviations: AML, acute myeloid leukemia; OR, odds ratio.

of MDS, but we found a nonsignificantly increased risk associated with pernicious anemia. In another small study (n = 84), an association between total autoimmune diseases and MDS was observed.[29]

A possible explanation for the observed associations between infectious and autoimmune conditions and risk of AML/MDS is that these diseases are premalignant manifestations that are caused by the immune disruption that precedes the development of AML/MDS. There are case reports that show co-occurrence of autoimmune diseases and AML/MDS.[30,31] However, because of the acute nature of primary AML, and because many of the risks were still significantly elevated more than 3 years before AML/MDS diagnosis, the premalignant explanation is not likely. We cannot entirely rule out that infection and autoimmunity are markers for an immune disruption that is an early part of the leukemogenic process. Clearly, these possibilities need additional investigation.

Our findings may be important for several reasons. Potentially, the underlying explanations for our findings may reflect the immune-related or inflammation-driven tumorigenesis from autoimmune conditions that leads to AML or MDS. Alternatively, the treatments given to patients with autoimmune disease (eg, corticosteroids, anti-inflammatory agents, and immunosuppressive agents) might play a role for the risk of AML and MDS. Also, there might be shared common genetic and/or environmental susceptibility in autoimmune diseases and AML and MDS.

Our study has several strengths, including its large size, which allowed assessment of a broad range of infectious and immune-related conditions, and high-quality data from Sweden in a stable population with access to standardized universal medical health care during the entire study period. Furthermore, the use of the nationwide, register-based, case-control design ruled out recall bias and ensured a population-based setting and generalizability of our findings. One could argue that AML and MDS are heterogeneous diseases, with age at diagnosis as one source of heterogeneity. In the population, AML incidence rates start to increase dramatically after age 40 years. However, our findings were consistent even in the youngest patients with AML/MDS (ie, those diagnosed before 40 years of age).

Limitations of our study include lack of clinical data, lack of validation of individual medical records, lack of information on potential confounders (although the study design ensured adjustment for sex, age, and geography), treatment, and absence of a systematic blinded validation of all AML/MDS diagnoses. Also, because of the nature of this hypothesis-generating study, one has to interpret our

Table 5. Personal History of Autoimmune Disease and Risk of MDS

Category or Condition	Participants				Latency 3 Years Before MDS Diagnosis			
	No. of MDS Occurrences (n = 1,662)	No. of Controls (n = 6,489)	OR	CI	No. of Occurrences	No. of Controls	OR	CI
Total autoimmune disease	133	263	2.1	1.7 to 2.6	91	220	1.7	1.3 to 2.1
Systemic involvement	40	93	1.7	1.2 to 2.5	33	81	1.6	1.1 to 2.4
Rheumatoid arthritis	36	82	1.7	1.2 to 2.6	29	82	1.6	1.0 to 2.4
Systemic lupus erythematosus	4	4	3.9	1.0 to 15.6	3	4	2.9	0.7 to 13.1
Sjögren's syndrome	3	3	3.9	0.8 to 19.4	3	1	11.7	1.2 to 112.9
Organ involvement	39	85	1.8	1.2 to 2.7	23	70	1.3	0.8 to 2.1
Pernicious anemia	10	22	1.8	0.8 to 3.7	2	19	0.4	0.1 to 1.7
Autoimmune hemolytic anemia	3	0	$P = .008$		1	0	$P = .204$	
Immune thrombocytopenic purpura	6	1	23.9	2.9 to 198.4	1	1	3.9	0.3 to 62.9
Myasthenia gravis	4	2	7.9	1.4 to 42.9	4	1	15.9	1.8 to 142.1
Polyarteritis nodosa	2	0	$P = .0$		2	0	$P = .04$	
Celiac disease	3	5	2.4	0.6 to 9.9	3	4	3.0	0.7 to 13.2
Wegener's granulomatosis	4	0	$P = .002$		4	0	$P = .002$	
Chronic rheumatic heart disease	5	18	1.1	0.4 to 2.9	4	15	1.0	0.3 to 3.1
Autoantibodies not detectable	62	107	2.3	1.7 to 3.2	40	87	1.8	1.3 to 2.7
Sarcoidosis	3	12	1.0	0.3 to 3.5	2	12	0.7	0.2 to 2.9
Crohn's disease	3	8	1.5	0.4 to 5.7	2	8	1.0	0.2 to 4.7
Ulcerative colitis	7	18	1.5	0.6 to 3.7	6	15	1.6	0.6 to 4.1
Polymyalgia rheumatica	18	36	2.0	1.1 to 3.5	11	24	1.8	0.9 to 3.7
Psoriasis	13	25	2.0	1.0 to 4.0	12	23	2.1	1.0 to 4.1
Giant cell arteritis	7	5	5.4	1.7 to 17.1	5	2	9.7	1.9 to 49.9
Aplastic anemia	11	4	10.8	3.4 to 34.0	1	1	4.0	0.3 to 63.7

NOTE. ORs were adjusted for categoric year of birth, date of diagnosis, sex, and county. When presented in square brackets, two-sided *P* values that were based on Fisher's exact test were given when no patient or control had the specified condition. Overall categories total to less than the sum of the individual categories because some individuals have more than one autoimmune disease.

Abbreviations: MDS, myelodysplastic syndrome; OR, odds ratio.

findings with caution because of the many immune-related conditions assessed. Although our study is large, some associations were based on small numbers. The use of inpatient data would be expected to lead to under-ascertainment of less severe forms of chronic immune-related conditions. Thus, our findings may apply mainly to severe forms of immune-related conditions. However, we also captured finding even if these conditions were not the primary diagnoses. Also, because the Inpatient Registry was started in 1964, childhood infections are not included. However, because personal history of immune stimulatory conditions was assessed similarly among the patients with AML/MDS and control participants, any underdiagnosis should be nondifferential, and any bias should be toward the null. We considered the effect of possible bias as a result of greater likelihood of patients with AML to have multiple different autoimmune or infectious conditions. We found that the overall patterns of association were present even when individuals with multiple different conditions were not included in the analysis. This indicates that multiple, chronic, immune-related conditions did not bias our results. We also found that autoimmune disease and infections are independent risk factors for AML/MDS. An inherent limitation of our study, which includes patients who were diagnosed with AML/MDS during a long study period, is that diagnostic criteria have evolved over time. The most important change was that 20% blasts were needed for AML diagnosis, whereas patients with 20% to 30% blasts were classified as MDS before 2001.[3] Because we included both conditions in the analyses, and because the risks were similar, this should not have had a major impact on our results. We also evaluated the risk in patients with AML who were diagnosed in 1990 or later, and the results were essentially the same (data not shown).

Furthermore, we cannot exclude the possibility that some of the patients with AML/MDS had a preceding malignancy that was not reported to the cancer registry. However, in our large, nationwide study on the ascertainment and diagnostic accuracy of lymphoproliferative malignancies that were diagnosed in Sweden, we found that the diagnostic accuracy and completeness was more than 93%.[16]

In summary, we found that a previous history of certain infections and autoimmune diseases increases the risk of AML and MDS. These findings raise the possibility that immune-related conditions might act as triggers for AML/MDS development. The underlying mechanisms may also be due to a common genetic predisposition or an effect of treatment for autoimmune conditions/infections. Future studies are needed to increase our understanding of the underlying biologic mechanisms of our findings.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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