Acute myeloid leukemia developing in patients with autoimmune diseases

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ABSTRACT

Therapy-related acute myeloid leukemia is an unfortunate complication of cancer treatment, particularly for patients with highly curable primary malignancies and favorable life expectancy. The risk of developing therapy-related acute myeloid leukemia also applies to patients with non-malignant conditions, such as autoimmune diseases treated with cytotoxic and/or immunosuppressive agents. There is considerable evidence to suggest that there is an increased occurrence of hematologic malignancies in patients with autoimmune diseases compared to the general population, with a further increase in risk after exposure to cytotoxic therapies. Unfortunately, studies have failed to reveal a clear correlation between leukemia development and exposure to individual agents used for the treatment of autoimmune diseases. Given the dismal outcome of secondary acute myeloid leukemia and the wide range of available agents for treatment of autoimmune diseases, an increased awareness of this risk and further investigation into the pathogenetic mechanisms of acute leukemia in autoimmune disease patients are warranted.

This article will review the data available on the development of acute myeloid leukemia in patients with autoimmune diseases. Possible leukemogeneic mechanisms in these patients, as well as evidence supporting the association of their primary immunosuppressive status and their exposure to specific therapies, will also be reviewed. This review also supports the idea that it may be misleading to label leukemias that develop in patients with autoimmune diseases who are exposed to cytotoxic agents as 'therapy-related leukemias'. A better understanding of the molecular defects in autoimmune disease patients who develop acute leukemia will lead to a better understanding of the association between these two diseases entities.

Key words: autoimmune disease, secondary leukemia, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, systemic lupus erythematosus.

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Introduction

The term 'secondary leukemia' is used to describe leukemia that did not develop as a primary or *de novo* process.[1] Secondary leukemia generally refers to leukemia developing in patients who have a history of exposure to various therapeutic agents as well as a history of antecedent myeloid stem cell disorders, such as myelodysplasia (MDS). Therapy-related acute myeloid leukemia (t-AML) is a term used to describe the former.[1] According to the World Health Organization (WHO), t-AML, therapy-related myelodysplastic syndrome (t-MDS), and myelodysplastic syndrome/myeloproliferative neoplasms (t-MDS/MPN) developing in patients who are exposed to cytotoxic agents are collectively classified as therapy-related myeloid neoplasms (t-MN).[2]

t-AML, which accounts for about 10% of all AML diagnoses, is a well-recognized complication in patients with primary malignant or non-malignant conditions after exposure to chemotherapy, radiotherapy, or immunosuppressive therapies.[3] Autoimmune diseases (ADs) are the most common non-malignant conditions associated with t-AML, accounting for 1.5% of t-AML cases.[4] The reported latency period between exposure to treatment for ADs and the development of t-AML is variable, ranging from a few months to several years and depends on the type of therapy, dose schedule, and cumulative dose, as well as patient-related factors.[3] The genetic and host risk factors potentially predisposing to the development of t-AML in ADs are currently the subject of intense research. Tumor cells need to evade the immune system to develop overt disease, thus defects in the immune system are recognized risk factors for cancer development.[5] In turn, patients diagnosed with diseases involving a defective immune system, or those receiving immunosuppressive therapies, are believed to be at high risk of developing acute leukemia.[6]

Literature search method

Patients with secondary acute leukemia most commonly

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develop AML rather than ALL.[7] Our research is, therefore, focused on AML cases. Since AML is a relatively rare disease, most studies available in the literature estimate AML risk in autoimmune diseases within a wider group of hematologic malignancies (e.g. acute and chronic myeloid leukemia, myeloproliferative diseases, and acute myeloid and lymphoid leukemia). All cases diagnosed as secondary acute leukemia associated with ADs, were identified by a Medline search, in bibliographies of articles, case reports, and meeting abstracts. All cases with available clinical data were collected and analyzed.

Autoimmune diseases

With the exception of rheumatoid arthritis and autoimmune thyroiditis, ADs are relatively uncommon, with a low incidence (90 per 100,000 person years) and low prevalence rates (3-7%) in Western countries.[8,9] Most ADs affect middle-aged women more than men, with considerable morbidity and mortality. Large, well-designed population-based case-control studies in patients with rheumatoid arthritis[10] and systemic lupus erythematosus (SLE) suggest that a number of factors might be implicated in the development of ADs. These include cigarette smoking, infection, hair treatment, hormonal treatment, occupational exposures, drugs and psychosocial stressors.[11-13] Together with reports on families and twins, these studies indicate that ADs may also result from the interaction of genetic and environmental factors.[14-19] Clinically, ADs are classified into systemic and localized organ specific forms. Systemic ADs include rheumatoid arthritis, SLE, systemic sclerosis, Sjogren's syndrome, scleroderma and dermatomyositis/polymyositis, while multiple sclerosis and inflammatory bowel diseases affect specific body organs. Autoimmune diseases exhibit variable courses with clinical remissions and exacerbations. Advanced cases have progressive courses with high morbidity and mortality. In the past decade, important progress has been made in the therapeutic approach to ADs, particularly with the development of biological drugs.[20] However, these diseases remain in most cases incurable.[8,9]

Autoimmune diseases and the risk of myeloid leukemia

Anderson *et al.* explored the association of myeloid malignancies with ADs by comparing 13,486 patients aged over 67 years with myeloid malignancies to 160,086 population-based matched controls using the SEER-Medicare database of Hematopoietic Malignancy Risk Traits (SMAHRT). The authors found that having an AD is associated with a significant increase in the risk of AML with odds ratios (OR) of 1.29, (95% CI, 1.2-1.39) and myelodysplastic syndrome (MDS) with OR of 1.50, (CI, 1.35-1.66). AML risk was significantly associated with rheumatoid arthritis (OR 1.28), SLE (OR 1.92), polymyalgia rheumatica (OR 1.73), autoimmune hemolytic anemia (OR 3.74), systemic vasculitis (OR 6.23), ulcerative colitis (OR 1.72) and pernicious anemia (OR 1.57).[21] This was confirmed in a recent study by Kristinsson *et al.* that included 9,219 patients with AML, 1,662 patients with MDS, and 42,878 matched controls from population-based central registries in Sweden. The authors of this study observed that a previous history of any autoimmune disease was associated with a 1.7-fold (95% CI, 1.5-1.9) increased risk of AML and 2.1-fold (95% CI, 1.7-2.6) increased risk of MDS.[22]

The association between rheumatoid arthritis and myeloid leukemia

Non-steroidal anti-inflammatory drugs (NSAIDs) are used as single agents in RA for mild, well-controlled disease. Disease modifying anti-rheumatic drugs (DMARDs), used in the treatment of rheumatoid arthritis, include corticosteroids, and immune response modulators (leflunomide, abatacept, and anakinra and TNF blockers). DMARDs are further divided into biological (anti-TNF agents) and non-biological subclasses. TNF-α is one of the most important regulators of inflammatory processes, thus a chimeric or humanized TNF-α inhibitor is a key anti-inflammatory targeted therapy in these diseases. The biological DMARDs include anti-TNF agents, such as etanercept, infliximab and adalimumab. Non-biological DMARDs include methotrexate (MTX), leflunomide, sulfasalazine, antimalarial (hydroxychloroquine), gold injections, d-penicillamine, minocycline, azathioprine (AZA) and cyclophosphamide (CTX). Non-biological DMARDs are used in early disease stages and combination therapy is recommended for more severe cases with progressive courses.[20]

Early case reports (in the 1970s) and small case series for AML and MDS developing in rheumatoid arthritis patients raised concerns about leukemia risk in these patients. Rheumatoid arthritis patients were exposed to azathioprine,[23,24] methotrexate,[25-27] alkylating agents (cyclophosphamide and chlorambucil)[28] and biological agents such as anti-TNF drugs.[29] Rosenthal and Farhi identified 8 cases of MDS/AML in the pathology records of the University of Cleveland and Emory University for autoimmune disease patients: 5 cases treated with methotrexate for rheumatoid arthritis, 2 cases treated with chlorambucil for Behcet's disease, and one case treated with cyclophosphamide for systemic lupus erythematosus. Exposure periods were between six months and over ten years, and cytogenetic data were available for 3 patients. One patient had t(8;21), one had complex karyotype and the third had inv(16) after methotrexate, chlorambucil and cyclophosphamide exposure, respectively. Outcome information was reported for 5 patients: 3 AML patients remained in remission for some years after bone marrow transplantation, one MDS patient died from infectious complications and the other MDS patient had evolution into AML.[30] A significant excess of leukemia risk in rheumatoid arthritis patients was described in early cohorts of cancer registries in Finland,[31] Sweden,[32] Denmark[33] and Birmingham.[34] This significant risk was further confirmed in a prospective cohort of 862 rheumatoid arthritis patients diagnosed between 1966 and 1974, and followed up for a mean of 17.4 years (P=0.027). Only 2 of 12 cases had been exposed to cyclophosphamide alone or in combination with azathioprine.[35]

The main data of large population-based studies exploring the risk of leukemia in rheumatoid arthritis are summarized in Table 1. The standardized incidence ratio is calculated by comparing the number of observed cases to what is expected in the general population as a control.

Four large population-based studies suggest an association between the risk of leukemia and rheumatoid arthritis in patients treated with non-biological DMARDs. In one study, the risk of leukemia was assessed in three cohorts of rheumatoid arthritis patients retrieved from the Swedish Cancer Registry. The study included three cohorts, one of early arthritis patients (recruited within

one year of rheumatoid arthritis onset), one of hospitalized patients with advanced disease and a third of patients treated with TNF blockers. A significant association between rheumatoid arthritis and the risk of AML was observed in the inpatient prevalent and early-arthritis incident cohorts.[36] In the second study, the rheumatoid arthritis cohort, derived from California's statewide discharge data set, both inpatient men and women with rheumatoid arthritis patients had a significant risk of being diagnosed with leukemia, with males at a substantially greater risk[37] compared to the general population. The Swedish Cancer registry was used in the third study which examined 42,262 hospitalized rheumatoid arthritis patients between 1980 and 2004. There was an overall increase in AML with further risk in patients diagnosed after 1999 and those under the age of 50 years. AML was also seen more during the first year after diagnosis with a standardized incidence ratio (SIR) of 4.88 for less than one year and 2.03 for 1-4 years.[38]

The fourth study analyzed the potential associations between individual DMARDs and the risk of developing hematologic neoplasms. This was a cohort of elderly patients (mean age 61.7 years) linked to the population data base of Quebec. The incidence rate of hematologic malignancies was 391.6 cases per 100,000 person-years in a cohort of 23,733 rheumatoid arthritis patients followed for a mean of 6.7 years. The risk of hematologic malignancy was significant in patients exposed to azacytidine and cyclophosphamide and borderline to methotrextae in an un-adjusted rate ratio in a case control design. Only with cyclophosphamide, the risk remained significant when the adjusted rate ratio was assessed.[39] Cyclophosphamide, a potent immunosuppressive agent whose use is restricted to severe cases of refractory rheumatoid arthritis, such as vasculitis, is known to be leukemogenic.[43]

Three additional population based studies examined leukemia/cancer risk, in patients treated with anti-TNF agents.[40-42] The risk of hematologic cancers in patients treated with anti-TNF therapy was compared to patients treated with any non-biological disease modifying agent in one study[41] and to methotrexate-treated patients in another.[42] Both studies observed no substantial increase in the risk of hematologic malignancies related to anti-TNF therapy. The short follow-up time (~2.5 year) in the anti-TNF cohorts was a limitation of both studies. Askling *et al.* reported one of the largest population-based studies on TNF blocker-associated cancer risk. Patients treated with anti-TNF (adalimumab, etanercept, and infliximab) were compared to biological-naive, a methotrexate, and a disease modifying combination therapy cohorts, as well as to the general population. The relative risk of cancer in anti-TNF treated patients was higher than in the general population that was statistically significant in the following 2-4 years with SIR of 1.25 (CI 1.01–1.56). However, the over-

Table 1. Calculated risk of leukemia developing in rheumatoid arthritis (RA) patients from population based studies.

RA[1] cohort	(Total n. patients)	Leukemia type	AML patient numbers	Calculated risk (SIR, HR, ARR,RR)[2]	95% CI,	Ref.
Prospective cohort	862	AML	12	SIR=2.47	1.12-4.69	35
Inpatient	53067	AML	68	SIR=2.4	1.9-3.0	
Early arthritis	3703	AML	4	SIR=4.3	1.2-10.9	36
TNF-B[3]	4160	Undefined leukemia	2	SIR=6.8	0.8 -24.7	
Total	84,475	All leukemias	178	Not calculated		
Males	19,239	All leukemias	68	SIR=1.65	1.29-2.07	37
Females	65,236	All leukemias	110	SIR=1.27	1.03-1.51	
Total RA cohort	42262	AML	52	SIR=2.40	1.79-3.15	38
Case	619	Leukemia	178	ARR for		
Control	6910			CTX[6]=1.84	1.24-2.73	
				MTX=1.12	0.93-1.34	
				AZA=0.07	0.74-1.54	39
				Antimalarials=1.12	0.93-1.34	
				Anti-TNF=1.92	0.49-7.5	
				Other DMARD=0.83	0.69-1.01	
Anti-TNF *vs.*	6366	All cancers	240	RR of Anti-TNF *vs.*		
General population	408048		30490	General population=1.14	1.00-1.30	
Etanercept	2216	All hematologic[7]	8	Frequency 11%		40
Adalimumab	899	All hematologic	4	15%		
Infliximab	3249	All hematologic	16	11%		
TNF-B[4]	757	AML (del 8)	1	SIR= 0	0 to 9.2	41
DMARD	800	Leukemia/myeloma	2	SIR=1.1	0.1 to 4.1	
Total	334237		22	SIR=1.3		
TNF-B *vs.* MTX[5]	1152 *vs.* 7306	Leukemia	19 *vs.* 3	HR 1.37		
Individual cohort:		Leukemia		Incidence rate	85-1.97	42
Pennsylvania	1142.8 *vs.* 105207	Leukemia	1 *vs.* 4	87.5 *vs.* 38	0.71-2.6	
New Jersy	14103 *vs.* 94061		1 *vs.* 5	70.9 *vs.* 53.2		
British Colombia	400 *vs.* 105433		1 *vs.* 10	249.7 *vs.* 94.8		

[1]Rheumatoid arthritis; [2]Standardized incidence ratio, hazard ratio, adjusted rate ratio, relative risk, respectively; [3]Tumor necrosis factor blocker; [4]Disease modifying anti-rheumatic drugs; [5]methotrexate; [6]cycophosphamide; [7]hematologic malignancies include leukemia, lymphoma and myeloma. The standardized incidence ratio is calculated by comparing the number of observed cases to what is expected in the general population as a control. Adjusted rate ratio is calculated by comparing incidence rate of the case to matched control.

all cancer risk including hematologic malignancies in the anti-TNF therapy cohort was no different from the other treatment groups. In addition, this risk was the same regardless of the duration of active anti-TNF therapy during the 6-year follow-up period.[40]

There is insufficient data linking secondary hematologic malignancies to higher mortality in rheumatoid arthritis patients. Two important studies attempted to answer this question. In the 2003 study by Wolfe *et al.*, the mortality due to leukemia/lymphoma was high in 3,501 rheumatoid arthritis patients.[44] The ratio between the observed mortality for leukemia/lymphoma to that expected was 1.78 and the rate per 100 patient deaths was 1.92 (95% CI 1.16–3.09). However, such a rise was not reproduced in a randomly selected cohort of 789 rheumatoid arthritis patients.[45] In this study, although there was an increased risk of hematopoietic cancers in rheumatoid arthritis patients, the overall mortality due to cancer was no greater than expected.

The association between inflammatory bowel diseases and myeloid leukemia

Inflammatory bowel diseases include Crohn's disease and ulcerative colitis. The incidence and prevalence of inflammatory bowel diseases have increased over the past decade. They affect adults under 30 years of age, with Crohn's disease affecting younger patients.[46-48] Ulcerative colitis affects men and women equally and is restricted to the colon, while Crohn's disease tends to affect women more than men and may affect any part of the gastrointestinal tract. The current medications used in the treatment of inflammatory bowel disease include a large number of immunosuppressive agents, non-biological and step-wise treatments, such as 5-aminosalycilic acid (5-ASA), and corticosteroids, azathioprine, 6-mercaptopurine or methotrexate. TNF blockers were approved for inflammatory bowel diseases in the late 1990s and have recently been used not only for advanced stage disease but also as front-line therapy in early disease.[47,49]

The first description of secondary AML in patients with inflammatory bowel disease was published in 1980.[50] Fabry *et al.* observed 5 AML cases among 400 ulcerative colitis patients treated over an 8-year period. This was followed by a number of case reports and case series that suggested an association between inflammatory bowel disease and hematologic malignancies, in particular Crohn's disease to lymphoma and ulcerative colitis to leukemia,[51-59] as summarized in Table 2. There are 18 case reports of AML developing in patients with inflammatory bowel diseases. Patients were treated with steroids (12 cases), salfasalazine (8 cases), azathioprine (3 cases), 5-aminosalycilic acid (3 cases) and 6-mercaptopurine (2 cases). The reported median survival was seven months (range 3 weeks-4 years). Survival exceeded two years in patients treated with intensive chemotherapy.

Large case series and population-based studies exploring the risk of leukemia in inflammatory bowel disease treated with different agents are summarized in Table 3.[60-65] For patients treated with non-biological agents, there are five large case series and population based studies that observed an association between hematologic malignancies and inflammatory bowel diseases, particularly ulcerative colitis.[60-64] The association was statistically significant in three of the studies.[60,61,64] AML frequency was 8.7 times higher than expected in a series of 734 ulcerative colitis patients. Again, the AML subtypes were skewed more towards AML-M3 (5 of 7) in this series who were treated mainly with sulfasalazine and steroids.[60] AML-M3 is a rare AML subtype and is fortunately associated with a high cure rate. Likewise in the second study, a significant approximately 7-fold increase in AML risk was observed among 1,248 ulcerative colitis patients who were followed for a mean of 18 years.[61] These early observations were subsequently confirmed in a population based study of 47,679 patients with inflammatory bowel disease. Patients were linked to 3 regional and a nationwide inpatient Swedish registry and were followed for up to 40 years. A significant excess in AML occurred in ulcerative colitis patients specifically in regional cohorts. Thirty-four cases of AML were observed within five years of follow up. Male sex and the period between the sixth and tenth year of follow up were associated with the highest risk of leukemia.[64]

For patients exposed to biological agents, such as anti-TNF agents, there are no large case series or population based studies estimating the associated leukemia risk in inflammatory bowel disease. However, in the 2006 post-marketing worldwide safety report for all patients exposed to TNF blockers, 74 cases of leukemia were identified: 23 after exposure to infliximab, 39 after etanercept, and 12 rheumatoid arthritis or Crohn's disease patients after adalimumab. Unfortunately, information about the total number of patients exposed to these agents as a denominator is lacking.[66] It is worth noting that in 2009, the FDA reviewed 147 post-marketing reports of leukemia in all patients using TNF blockers. Of these, acute myeloid leukemia was seen in 44 cases. Of the total 30 deaths, 26 were due to leukemia. The average time to onset of secondary leukemia was within the first 1-2 years of therapy. The FDA added a warning to the current information regarding prescription of TNF blockers about malignancies in general, but this does not specifically mention leukemia.[67]

With regards to the leukemia related mortality rate in patients with inflammatory bowel disease, four studies reported increased mortality rate in ulcerative colitis patients, two of which reached statistical significance. Additionally, a 5-fold increase in mortality rate due to AML was observed among 1,248 ulcerative colitis patients compared to the general population with standardized mortality rate (SMR) of 5.3 (95% CI 1.7–12.3).[68] Similarly, in an Italian study of 2,066 ulcerative colitis patients, a statistically significant excess death rate from hematologic malignancies, mainly lymphoma and myeloma, was reported with SMR of 2.8 (95% CI 1.0–6.1).[69] However, in two ulcerative colitis cohorts, the significance of such an increased risk could not be confirmed with SMR of 1.43 (95% CI 0.02-7.9), one death from leukemia out of 689 in the first cohort, and SMR of 3 (95% CI 0.4–11), 2 deaths due to leukemia out of 62 in the second study.[70,71] Details of leukemia subtypes, treatments or causes of death are beyond the scope of these studies.

The association between multiple sclerosis and myeloid leukemia

Multiple sclerosis is a chronic autoimmune demyelinating disease of the central nervous system characterized by variable periods of relapse and remission of neurological symptoms with progressive disability over time. Patients whose disease fails to respond to first-line therapy using

disease-modifying treatment, like interferon beta (IFN-β) and/or glatiramer acetate (GA), may be considered for second-line treatments, such as mitoxantrone or natalizumab.[72,73] Mitoxantrone was the first immunosuppressive drug approved in the US and Europe as a single agent for the treatment of aggressive relapsing–remitting or progressive multiple sclerosis.[74] Mitoxantrone is the topoisomerase II (topo-II) inhibitor most frequently associated with development of t-AML.[75,76]

Acute myeloid leukemia is a well-known sequel of multiple sclerosis patients, a in particular those treated with mitoxantrone.[75,76] While few secondary AML cases in multiple sclerosis were mainly exposed to chorambucil, azathioprine or INF-beta(77-79), the majority occurred after exposure to mitoxantrone. The first case report of t-AML (M3) in a multiple sclerosis patient was published in 1998.[80] Subsequently, a number of case reports and case series were published on t-AML in mitoxantrone treated patients,[81-96] as summarized in Table 4.

Larger series of patients with multiple sclerosis treated

Table 2. Literature review of acute myeloid leukemia in inflammatory bowel disease (IBD) patients.

IBD	N. patients	Age[1]/ sex	IBD treatment	AML subtype	Latency [2] (months)	AML treatment	Overall survival (months)	Ref.
CD[3]	1	17/M	Salfasalazine	AML-M3	15	Daunorubicin-Ara-c[4] -6MP	4	51
CD	1	13/M	Steroids-AZA[5]-6-MP[6]	AML1	216	Daunorubicin-Ara-c	6	
CD	1	33/M	Salfasalazine	AML-M4 inv16	120	HDCT [7]	Alive in CR> 34	52
CD	1	32/M	Steroids-Salfasalazine	AML-M5b (-11q)	108	HDCT	Alive in CR> 22	
CD	1	36/F	Steroids-Salfasalazine-AZA	AML-M5a	22	3&7[8]-HDCT	7	
UC[9]	1	34/F	Steroids-Salfasalazine	AML- M5	228	CTX[10]-VCR[11]-Ara-c	Alive in CR>12	
CD	1	47/F	Steroids-Salfasalazine	AML-M4	84	VCR- 6-MP-Ara-c	4	53
UC	1	9/M	Steroids-Salfasalazine	AML	168	Chemotherapy	16	
CD	1	9/M	Steroids-Salfasalazine	AML	816	Chemotherapy	5	
CD	1	18/M	Steroids	AML	12	Immediate death	<1	54
CD	1	15/M	Not reported	AML	48	Chemotherapy	10	
CD	1	60/F	Salicylazosulfapyridine	AML-M4	60	VP16[12]-TG[13]-idarubucin 6-6-MP-MTX[14]	11	
CD	1	45/M	salicylazosulfapyridine – 5-aminosalycilic acid	AML-3p	24	Daunorubicin-Ara-c -TG	3	55
CD	1	70/M	Steroids	MDS-EB (25% blasts-WHO 2008AML)	Concomitant	Supportive	2	56
CD	1	67/M	5-aminosalycilic acid-steroids	AML -M3	132	Immediate death	0.75	
CD	1	29/F	5-aminosalycilic acid-steroids	AML-M3	96	Hyroxyurea-imatinib mesylate	Alive in CR>48	57
CD	1	42/F	6-MP	AML (del7)	20	Bortezomib, Daunorubicin -Ara-c	-	58
CD	1	43/F	Steroids-AZA	AML-M1	1	Idarubicin-Ara-c	Alive in CR >12	59

[1]Age at IBD; [2]latency period calculated from SLE diagnosis to leukemia development; [3]Crohn's disease; [4]cytosine arabinoside; [5]azathioprine; [6]6-mercaptopurine; [7]high-dose chemotherapy; [8]danurubicin (3 days) and Ara-c (7 days); [9]ulcerative colitis; [10]cyclophosphamide; [11]vincristine; [12]etoposide; [13]thioguanine; [14]methotrexate

Table 3. Calculated risk of leukemia developing in inflammatory bowel disease (IBD) patients from large case series and population based studies.

IBD cohort	Total n.	IBD treatment	AML subtype	N.	Calculated risk (IRR,SIR)[1]	Significance	Ref.
IBD total	1961		AML	7			
UC[2]	734		AML-M3	5	IRR= 8.70		60
			AML-M1	1		*P*<0.001	
CD3	1227	Sulfasalazine & steroids	AML	1	IRR= 0.76		
UC	1248	Not reported	AML	3	SIR= 6.6	*P*=0.01 95% CI 1.4-19.3	61
IBD Total	5529		Leukemia/myeloma	7	IRR= 0.91	95% CI 0.42-1.96	
CD	2857	Not reported	Leukemia/myeloma	3	0.79	0.24-2.54	63
UC	2672		Leukemia/myeloma	4	1.02	0.37-2.86	
IBD:	47679		AML	34	SIR	95% CI	
UC/regional	4467		AML	9	2.53	1.2-4.8	
UC/inpatients	20036	Not reported	AML	19	1.53	0.9-2.4	64
CD/regional	3561		AML	2	0.89	0.1-3.2	
CD/inpatients	19024		AML	84	0.51	0.1-1.3	
IBD total	550		AML	1			
CD	380	6MP	AML	1	Incidence=0.11/1000		65
UC	170		-	-			

[1]Incidence rate ratio, standardized incidence ratio, respectively; [2]Ulcerative colitis; [3]Crohn's disease. IRR and SIR are calculated by comparing the number of observed cases to what is expected in the general population as control.

with mitoxantrone consistently show an excess in AML risk, particularly of the promyelocytic subtype (M3). Acute promyelocytic leukemia is a highly curable disease, yet it is associated with high rates of early hemorrhagic death if not promptly diagnosed and treated. Therefore, early recognition of AML-M3 in patients at risk and proper management are critical. In 2002, Ghalie *et al.* reviewed 1,378 MS patients treated with mitoxantrone. Patients were exposed to a mean cumulative mitoxantrone dose of 60 mg/m^2 and were followed up for a mean of 36 months. The authors found the t-AML rate was found to be relatively low (0.15%).[97] Meanwhile, in a post-marketing report for mitoxantrone-treated multiple sclerosis patients from 2003 through 2007, 39 cases of acute leukemia were identified. The mean age of leukemia patients was 48.2 years and 28 years for men and women, respectively. The mean cumulative dose of mitoxantrone was 83.2 mg/m^2 (range 48-135). Acute promyelocytic leukemia represented 33.3% of French American British Classification (FAB) subtypes. The outcome of multiple sclerosis patients was worse when DNA-damaging antineoplastic agents, cytotoxic drugs, or escalating doses of anthracyclines were added to the therapeutic regimens. Therefore, caution should be used while prescribing these agents to multiple sclerosis patients.[98] In a 2009 preliminary report of 35 Italian centers, 21 cases of acute leukemia were identified among a cohort of 2,854 multiple sclerosis patients. Mitoxantrone dose-dependent risk was observed with an incidence rate ratio of 1.84 at cumulative doses below 60 mg/m^2 and 2.74 at doses over 82.4 mg/m^2. The main AML subtype in this study was myelomoncytic (M4) (19.0%). The clinical outcome of leukemia patients in this series was again not encouraging.[99]

Pascual *et al.* prospectively studied the rate of AML in two Spanish cohorts, from Valencia (n=142) and from Catalonia (n=88), of mitoxantrone treated multiple sclerosis patients. The cummulative incidence and incidence density of AML for the Valencian cohort were 2.82 and 0.62% respectively; and 2.27 and 0.44% for the Catalonian cohort. The latency period between treatment discontinuation and AML ranged from one to 45 months in both cohorts. There was no association between AML occurrence and dose, age at the beginning of the disease or at beginning of the treatment, disease duration, gender or concomitant medications. The authors further compared the cumulative incidence and incidence density of this

Table 4. Literature review of acute myeloid leukemia in multiple sclerosis (MS) patients from case series and population based studies.

MS cohort total n.	N. AML cases	Age[1]/sex	AML subtype	MS[2] therapy (MTZ3 dose mg/m^2)	Latency (months)	AML therapy	Status at last FU (months)	Ref.
59	1	34/F	AML-M4eo(inv 16)	AZA –MTX[4]-MTZ (72)	20	DCE-auto-SCT[5]	In CR at 14	81
-	1	28/F	APL	MTZ (120 total)	-	ATRA	In CR>35	82
-	1	43/F	APL	IFN-β[6]-steroids-MTZ (60)	26	AIDA	In CR>3	83
255	1	49/F	APL	MTZ (80)	32		3 days	84
304	1	46/M	AML-M1 t(8;21)	CTX-MTZ (84)	38	Chemotherapy	In CR at 26	85,86
644	1	45/F	AML-M4eo(inv 16)	MTZ (48)	42	CHT-allo-SCT	In CR at 24	87
25	11	47/F	APL	MTZ (12)-IFN-β	30	Immediate death	2 days	88
27	1	33/M	APL	MTZ (66)-GA[7]	49	Chemotherapy	In CR at 12	89
250	2	21/F 37/F	APL APL	IFN-β -MTZ (120) MTZ (144)	27 22	AIDA-auto-SCT AIDA-auto-SCT	In CR at >12 Alive in CR at >12	90
100	1	37/F	AML-M4	MTZ (70)	20	CHT-SCT	In CR at 70	91
176	5	-/F -/F -/F -/M -/F	APL APL APL APL AML-M4	MTZ (60 total) MTZ(22.5 total) MTZ (130 total) MTZ (110 total) -	Median 40 months	ATO-auto-SCT	CR in 4/5 1 relapse and death at 41 months	92
61	2	56/F 50/M	APL AML-M2 t(8;21)	IFN-β-MTZ (96 mg/m^2) IFN-β-MTZ(84 mg/m^2)-MTX	31 28	AIDA Refused therapy	In CR at 4 years <1 month	93
230	5	52/F 23/M 59/F 33/F 44/M	APL APL APL APL APL	AZA-MTZ (30) MTZ-IFN-β (100) MTZ (70) MTZ (60) IFN-β-MTZ (159)	23 3 11 1 45	- 	Death In CR at 8 months In CR at 6 months Death In CR at 10 months	94
152	3	44/F 63/M 32/F	APL APL APL	INFb-GA-MTZ (96)-MMF[8]-CTX- MX Steroids IFN-β-MTZ (48)-MMF Steroids-IFN-β-MTZ (90)-GA-MMF-CTX	45 60 29	AIDA AIDA AIDA	CR CR CR	95
108	2	-	AML AML	MTZ (72 mg/m^2) MTZ (108 mg/m^2)	-	-	Death Death	96
1378	2	24/F 36/M	AML-M5 APL	MTZ (70) MTZ (50)	20 60	Danuorubicin-Ara-c -	8 In CR at 12	97

[1]*Age at AML, APL;* [2]*multiple sclerosis;* [3]*mitoxantrone;* [4]*methotrexate;* [5]*daunorubicin-cytarabine-etoposide;* [6]*interferon beta;* [7]*glatiramer acetate;* [8]*mycophenolate mofetil.*

cohort with the 32 t-AML cases from nine previously reported series. Latency period range was 1-60 months. The calculated incidence varied from 0.15 to 0.80% and main AML subtype was promyelocytic (57.1%). Furthermore, the incidence of acute leukemia did not vary significantly in the years since 2001, with 2 to 5 cases reported per year.[94] Ellis *et al.* reported an acute leukemia incidence of 0.33% (risk of 1:333) in multiple sclerosis patients. This frequency is 100 times higher than expected for *de novo* leukemia in a healthy population (0.03% by 70 years of age). However, this rate is still lower than that reported for patients who are treated for primary cancer with combination chemotherapy (2–12%).[100] Again APL was the most common subtype representing 46.4% of cases. About 80% of these cases were exposed to mitoxantrone at acumulative doses exceeding 60 mg/m^2.

In 2010, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology re-evaluated and reviewed incidence rates for acute leukemia occurring in multiple sclerosis patients. The overall incidence of acute leukemia in patients treated with mitoxantrone was found to be 33 of 4,076 (0.81%), ranging from 0.15 to 2.8%. The majority of cases was APL and occurred within three years of mitoxantrone treatment.[101] The previous studies and reports collectively showed a high incidence of AML in multiple sclerosis and of AML-M3 after mitoxantrone exposure. Long and close follow up for hematologic changes in multiple sclerosis patients, particularly for those exposed to cytotoxic agents, should be part of their management.

Recent reports found that the outcome of AML in multiple sclerosis patients was not inferior compared to *de novo* cases. The reported overall mortality of acute myeloid leukemia developing in mitoxantrone exposed multiple sclerosis patients was 24%, similar to that of *de novo* AML.[102] Our group recently reported the clinical features and treatment outcome of 33 patients with multiple sclerosis who developed AML-M3, the most frequently reported subtype in these patients. Thirty patients had been previously exposed to mitoxantrone. Twenty-nine (90%) patients achieved hematologic remission after all-trans retinoic acid (ATRA) and chemotherapy or arsenic trioxide and ATRA. The 5-year cumulative incidence of relapse and overall survival were 23 and 68%, respectively,[103] i.e. comparable to that of *de novo* APL.[82,104] However, the availability of alternative therapies to mitoxantrone associated with less severe toxicities (e.g. interferon-alpha and glatiramer acetate) should lead physicians to weigh the benefit against the potential harm of mitoxantrone for each individual patient with multiple sclerosis.[101]

The association between systemic lupus erythematosus and myeloid malignancies

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that may affect any body organ. The disease affects about 250,000 in the USA and is more common in women of childbearing age. It has a course of remission and exacerbations with a 10-year survival rate exceeding 90%.[105] Treatment recommendations depend on the severity of the disease. In milder disease forms, NSAIDs, hydroxychloroquine or short steroid courses are effective. In severe forms, more aggressive immunosuppression is recommended, including methotrexate, cyclophosphamide, azathioprine and mycophenolate.[106]

Similar to other ADs, the association between systemic lupus erythematosus and myeloid malignancies was initially suggested from case reports[23,24,107-120] and small case series which are summarized in Tables 5 and 6. On reviewing the literature, we identified 22 cases of AML developing in systemic lupus patients reported between 1967 and 2009. Median age was 42.5 years (range 10-77 years) and females made up 14 of 22 cases. AML was classified as AML-M4 in 4 cases, AML-M2 in 3 cases, AML-M6 in 2 cases and AML-M3, AML-M5 and AML-M7 were diagnosed in one case each. The remaining 9 cases did not have a defined subtype. The main exposure was to azathioprine in 11 patients while exposure to cyclophosphamide was noted in 5 patients. The median latency period to AML was 44 months (range 9-138). The majority of AML patients received only supportive care with poor outcome. With high-dose chemotherapy and stem cell transplantation, some patients achieved long remissions (Table 5).

There are three large population based studies estimating the risk of malignancies in systemic lupus erythematosus patients (Table 6). Bernatsky *et al.* reported an increased risk of all hematologic malignancies among an international cohort of 9,547 SLE patients. Patients were followed for eight years and the calculated leukemia standardized incidence ratio was 1.89 (95% CI 0.76–3.88).[121]

Tarr *et al.* observed that 13.5% of 860 SLE patients (771 women and 89 men) developed hematologic cancer within ten years of diagnosis. Hematologic cancers were observed at a higher number than expected (SIR of 1.31, 95% CI 0.424–3.071). Median age was 33 years (range 16-64 years) and 47 years (range 20-73 years) at time of lupus and cancer diagnoses, respectively. The principle exposure was to cyclophosphamide (7 cases), azathioprine (8 cases), cyclophosphamide and azathioprine (4 cases), methotrexate (one case) cyclosporine-A (one case), chloroquine (6 cases) and corticosteroids alone (9 cases). No association between exposure to a specific therapy and the development of malignancy was observed in this study.[122]

In the third study, risk factors for developing myeloid leukemia in SLE were studied in 5,715 hospitalized patients from the Swedish national registry and followed from 1964 through 1995. Except for preceding leukopenia, factors such as age, sex, disease duration and other SLE features were not significantly associated with leukemia development. Furthermore, the possibility that AML developing in these patients was therapy-related is unlikely since the study did not find any difference in the frequency of cytotoxic exposure between cases and control cohorts.[120]

In a retrospective analysis of death causes in 300 SLE patients registered at the Bloomsbury (Rheumatology-Unit SLE) clinic between 1978 and 2000, the most common cause of death was malignancy (20%).[123] Leukemia or hematologic cancer associated mortality rates were not estimated. However, a significant increase in hematologic cancer related mortality was reported in 9,547 SLE patients observed for an average of 8.1 years. Standardized mortality rate for hematologic malignancies (excluding NHL) was 2.1 (95% CI 1.2–3.4), thus double the risk in the general population.[124] Again, the overall mortality ratio was 19% and cancer-related mortality ratio was 2% among 860 SLE patients (771 women and 89 men). In this series, hematologic malignancies were third in frequency after breast and gastrointestinal cancers.[122] These studies were not specifically designed to estimate

Table 5. Literature review of acute myeloid leukemia in systemic lupus (SLE) patients.

Age[1]/Sex	SLE therapy (total dose gm)	AML subtype	Latency (months)[2]	AML treatment	OS (months)	Ref.
57/F	Steroids	AML	60	Supportive-6MP[3]	1	107
25/F	AZA[4]	AML-M4	86	-	-	108
25/M	Steroids-AZA (52)	AML-M4	10	Supportive	2	23
31/F	Steroids-AZA (273)	AML-M4	77	Supportive-steroids	2	109
55/F	Steroids	AML-M6	25	Supportive	Death in few months	110
70/M	Azaptopazone	AML	12	Ara-C-VCR[5]-prednimustine	1.5	111
10/F	-	AML	10	Steroids-6-MP-VCR	5	112
67/M	-	AML	20		Death in few months	113
24/M	AZA (40)	AML	9		Death in few months	
67/F	Steroids-CTX(4)[6]	AML-M2	12	Daunorubicin-Ara-C-thioguanin	2	114
35/F	Steroids	APL	41	-	Death in few months	115
32/F	Steroids-AZA (30), CTX (27)	AML-M4eo (inv16)	23	-	-	116
68/F	No previous treatment for SLE	AML-M7 complex karyotype	48	Refused	1	117
23/F	No AZA	AML	108	Auto-SCT	30	118
44/F	CTX(1.7)-AZA (37)	AML-M2	54	HDCT	Death in few months	24
41/F	Steroids-AZA(89)	AML-M4	96	HDCT	Alive in CR > 1 yr	
36/M	CTX (5.4g) AZA (300g) Cyclosporine Hydroxychloroquine	AML-M6(del7)	108	Allo-SCT	Alive in CR >5 yrs	119
65.5/M	No AZA	AML	30[7]	-	14	120
29/F	AZA(55)	AML	71[7]	-	6	
52/M	No AZA	AML2	138[7]	-	<2	
77/F	No AZA	AML	47[7]	-	2	
50.5/M	AZA (50)-CTX(120)	AML-M5	110[7]	-	18	

[1]Age at AML; [2]latency period calculated from start of therapy if specified, otherwise from SLE diagnosis; [3]mercaptopurine; [4]azathioprine; [5]vincristine; [6]cyclophosphamide; [7]from SLE.

Table 6. Calculated risk of leukemia developing in systemic lupus erythematosus (SLE) patients from large case series and population based studies.

SLE total n.	Leukemia type	N. cases	Calculated risk (SIR, OR)[1]	95% CI	Ref.
5715	Myeloid leukemia	8	OR for exposure to oral steroids 1.2 AZA[3] 0.8 CTX 0.4	0.89-1.5 0.1-4.1 0.1-3.8	120
9547	Hematologic malignancies[2]	15	SIR 2.1	1.2-3.4	121
860	Hematologic malignancies	5	SIR 1.31	0.424-3.071	122

[1]Standardized incidence ratio, odds ratio, respectively; [2]Hematologic malignancies include leukemia, lymphoma and myeloma; [3]azathioprine, cyclophosphamide. The SIR is calculated by comparing the number of observed cases to what is expected in the general population as control.

the outcome of SLE patients who developed acute leukemia. Therefore, it is difficult to draw any conclusions about secondary leukemia related mortality in SLE patients.

Systemic sclerosis and myeloid malignancies

Systemic sclerosis is a chronic multisystem disorder characterized by collagen accumulation in skin and visceral organs of unknown etiology. Few cases of hematologic malignancies have been reported in these patients. Some case reports were described as concomitant to systemic sclerosis. Hematologic malignancies were in the form of CML,[125-127] CLL[128,129] large granular lymphocyte leukemia,[130] hairy cell leukemia,[131-133] multiple myeloma,[134,135] lymphoma,[136-138] ALL[139] and AML.[140,141] The main reported medication in these cases was D-penicillamine, in particular with CLL.[142,143] Since these are sporadic case reports, the apparent associations with any therapy remain unproven.

Mechanisms underlying autoimmune diseases in common with cancer pathogenesis

Nearly all cancers develop due to mutations in genes responsible for the regulation of cell growth, differentiation, apoptosis and repair. Defects in repair and apoptosis are also established mechanisms in ADs.[144-146] Mutations in the tumor suppressor gene p53 are frequent in autoimmune diseases, such as rheumatoid arthritis and inflammatory bowel disease.[147] Fas, a death receptor belonging to the tumor necrosis factor receptor superfamily, is defective in ADs and is also linked to cancer susceptibility.[144,148,149] The phosphatidylinositol 3-kinase (PI3K)/Akt (protein kinase B,PKB)/mammalian Target Of Rapamycin (mTOR) signaling pathway, known to be altered in leukemia,[150,151] is also involved in the pathogenesis of some ADs.[152-156] The mitogen-activated protein kinases (MAPKs) pathway mediates signal transduction in response to various stimuli, including stress and inflammation. Three groups of MAPKs include the extracellular-regulated kinases (ERKs) and the stress-activated protein kinases (SAPKs) p38 and c-Jun NH2-terminal kinase (JNK).[157] They regulate control gene expression, cell division, cell survival, apoptosis,

metabolism, differentiation as well as inflammation.[158] Deregulated Ras/Raf/mitogen-activated protein kinase (MEK)/ERK pathway is involved in AML[158] and immune disorders such as IBD.[159] Moreover, leukemia associated with mutations in this pathway are resistant to inhibitors specific to this pathway, as well as to inhibitors of other pathways like the PI3K/PTEN/Akt/mTOR.[151]

Both specific and non-specific immune responses play a major role in controlling the growth of malignant cells (tumor surveillance).[160,161] Any disruption of this system by a primary pathological or iatrogenic process will provide the opportunity for abnormal cells to evade surveillance and progress into malignancy. In addition, the interaction between tumor cells and the host microenvironment of stromal cells and inflammatory/immune cells contributes to a complex inflammatory signaling process that enhances tumor progression.[162,163] For example, NF-kappaB a major player in the pathogenesis of autoimmune diseases, such as rheumatoid arthritis, is involved in cancer and leukemia development.[164] Furthermore, chemokines and cytokines produced by inflammatory cells have a powerful pro-tumor activity.[165] Early in the neoplastic process, inflammatory cells facilitate genomic instability, promote angiogenesis and create an attractive environment for tumor growth. Successively, tumor cells direct inflammatory mechanisms which favor the dissemination of neoplastic elements via lymphatics and capillaries, evading host defence. This is achieved by remodelling the extra-cellular matrix and regulating selectin–ligand interactions, as well as metalloproteinase production and chemokine functions and receptors.[165]

T-cell responses are implicated in the pathogenesis of lupus, rheumatoid arthritis and other autoimmune diseases.[166] Interestingly, Young suggested a role for cytotoxic lymphocyte attack in individuals with defective immune system in triggering apoptosis of hematopoietic stem cells. In some patients, a few cells may survive cytotoxic lymphocyte attack and retain a residual DNA injury.[167] Permanent genomic alterations, such as point mutations, deletions, or rearrangements, may accumulate over years ultimately resulting in clonal outgrowth and leukemia.

The carcinogenic potentials of immunosuppressive and chemotherapeutic agents may act synergistically. However, with the exception of azathioprine, cyclophosphamide and mitoxantrone, there are insufficient data on the carcinogenic potential of other immunosuppressive agents such as steroids and anti-lymphocyte globulin.[168-171] Recent studies from our group have shown that DNA breakpoints (hotspots) are tightly clustered in an 8-bp region within *PML* intron 6 in MS patients who developed APL after mitoxantrone. *In vitro* cleavage experiments showed that this region contains a preferential site of mitoxantrone-induced cleavage by topoisomerase II.[76,172] Individual genetic variations in drug metabolism and response to DNA damage[3,173] play major roles in cancer development after cytotoxic exposure. Individual genetic variations in resistance to DNA damage by means of repair and/or apoptosis are just as critical to leukemogenesis. For example, increased susceptibility to develop promyelocytic leukemia in patients with multiple sclerosis receiving mitoxantrone was found to be linked to genetic variants in DNA repair and drug-metabolizing enzymes that result in impaired detoxification of chemotherapy or inefficient repair of drug-induced genetic damage.[75]

Conclusions

Although the evidence regarding the risk of hematologic malignancies, and in particular lymphoma in Ads has been growing, few studies have focused on AML. Therefore, the importance of this complication in patients with ADs is not well-known. This is the first systematic review of published data regarding the risk of AML in individual autoimmune diseases. Most studies investigating the association between hematologic malignancies and ADs revealed an excess AML risk in these patients. However, this risk did not reach statistical significance in some of the studies because AML is a rare disease and the studies were not designed to assess AML risk. For rheumatoid arthritis, the risk of AML was significantly higher than in the general population in two large population based studies.[36,38] The lack of treatment details in these studies, however, limited our ability to reach any conclusion about their leukemogenic role. For inflammatory bowel disease, AML risk was reported to be significantly high in ulcerative colitis patients in two studies.[36,64] Again, the evidence currently available means it is not possible to attribute such cases to therapy.

Multiple sclerosis patients are known to be at risk of developing APL, particularly those treated with mitoxantrone. However, not all multiple sclerosis patients treated with mitoxantrone develop secondary leukemia while others develop leukemia without mitoxantrone exposure.[71] Therefore, patient (host) related factors seem to play a fundamental role in the pathogenesis as described previously. The risk of myeloid leukemia was found to double in an SLE cohort.[120] However, studies addressing the leukemogenic potential of SLE therapy gave conflicting results. While patients were observed to develop malignancy without previous exposure to cytotoxic or immunosuppressive agents,[174] others reported an increased risk after exposure to immunosuppressive drugs.[175,176] With the exception of multiple sclerosis, no studies have investigated the mechanism underlying leukemogensis in autoimmune diseases.

The fact that patients with various ADs as well as those given immunosuppressive therapy for other reasons, such as those receiving organ transplants, are at very high risk of cancer development, supports the hypothesis that the primary defect is related to the host. Additionally, not all cancer patients exposed to cytotoxic agents develop leukemia, and leukemia develops after cancer in patients with no exposure.

This review also supports the idea that there is insufficient evidence to label leukemias that develop in patients with ADs who are exposed to cytotoxic agents as 'therapy-related leukemias'. Hence, one should exercise caution when using the term 'therapy-related leukemia' as it can bias our attitudes when trying to understand the association between these two types of diseases. Our focus should be on investigating the molecular defects in the autoimmune diseases, including defects in immunity, DNA repair, and apoptosis in these patients rather than studying only drug mechanisms that lead to leukemogenesis. In conclusion, the precise pathophysiology underlying ADs and its link to cancer development remains unclear. Finally, the risk of AML in AD patients warrants more attention, as it provides a model for investigating the role of defective immunological mechanisms in leukemogenesis.

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