Autoimmunity, Clonal Hematopoiesis, and Myeloid Neoplasms

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KEYWORDS

• Autoimmune disease • Myeloid neoplasms • Clonal hematopoiesis • DMARDs

KEY POINTS

- Clonal hematopoiesis is associated with chronic inflammation, endothelial dysfunction, and increased all-cause mortality, and may be linked to autoimmune disease.
- Autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus, have been associated with an increased risk of myeloid neoplasms.
- Myeloid neoplasms have also been associated with autoimmune diseases and systemic inflammatory syndromes.
- Treatment of autoimmune diseases can give rise to therapy-associated myeloid neoplasms.

INTRODUCTION

The associations between rheumatologic disorders and malignancy have been well described in the literature. The causes vary from rheumatic comorbidity, unchecked chronic inflammation, to adverse effects of immunosuppressive agents. Certain rheumatologic disorders, including dermatomyositis, systemic sclerosis (SSc), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Sjögren syndrome (SS), have strongly been linked with malignancy.[1] Enhanced screening is usually undertaken, supported by other clinical manifestations, additional risk factors for malignancy (family history, cigarette smoking, and so forth), and disease-specific autoantibodies (anti-transcriptional intermediary factor 1 antibody/TIF1-Ab positivity in dermatomyositis[2] and RNA polymerase 3 positivity in SSc).[3] There is a lack of consensus for specific algorithms and the debate continues while further studies are conducted.

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The expanding use of immunotherapy (immune checkpoint inhibitors) for treatment of malignancy has led to multiple adverse effects, among which rheumatic manifestations are common, including severe manifestations such as myositis and vasculitis.[4] Rheumatic manifestations can be a precursor or can accompany precursor states associated with myeloid neoplasms (MNs).

This complex interplay affects survival, quality of life, and therapeutic management. Although several of these associations have been researched in detail and hypothesis proved, the interaction between autoimmunity and hematologic malignancy has been less well defined. One major challenge is the overall rarity in incidence of most MNs and rheumatic autoimmune diseases, RA being the main exception. The lack of large randomized studies can provide challenges in clinical care of these patients (management, screening, and prognosis). This article explores what is currently known of these associations in detail, namely the links of MNs with rheumatic diseases, along with the impact of therapeutic interventions for autoimmune disease; that is, disease-modifying antirheumatic drugs (DMARDs) and biologic agents with MNs.

RHEUMATOLOGIC ASSOCIATION WITH MYELOID NEOPLASMS

Disease Subsets

Clonal hematopoiesis

Before exploring MNs, this article covers novel premalignant hematologic conditions (ie, clonal hematopoiesis [CH]) and its association with autoimmune disorders. CH is defined as the acquisition and propagation of somatic mutations in hematopoietic stem cells in people with normal blood counts.[5,6] When these mutations are putative driver mutations, involving leukemia-associated genes, with a variant allele frequency greater than or equal to 2%, this is termed CH with a putative driver or CH of indeterminate potential (CHIP).[5] When CH can be detected in the context of low blood counts and the absence of a defining bone marrow disease state, this is called clonal cytopenia of undetermined significance. CHIP is an age-dependent phenomenon, with the incidence being less than 1% before the age of 40 years and greater than 30% beyond age 80 years.

Several genetic studies in apparently healthy individuals (from a hematological perspective) have identified somatic clonal mutations that predate the development of clinical manifestations. These CHIP states are associated with a low risk of evolution to MNs (dependent on the driver oncogene) but are associated with an increased risk of cardiovascular disease and all-cause mortality.[6,7] Importantly, the risk of cardiovascular disease in individuals with CHIP is maintained when traditional risk factors (smoking and a family history of atherosclerotic cardiovascular disease) are excluded. The hypothesis behind this phenomenon is that CHIP commonly involves mutations in epigenetic regulator genes, *DNMT3A*, *TET2*, and *ASXL1*. These mutations affect monocytes/macrophages, leading to an inflammatory phenotype with associated cytokine release and endothelial dysfunction.[6] Given an increased cardiovascular risk in most rheumatic diseases compared with the general population, it is speculated that this risk is in part caused by coexistent CH.

The impact of CHIP in RA has been evaluated in 1 single-center study comparing patients with RA (median age, 58.5 years), healthy controls, and patients with aplastic anemia. A prevalence of 17% was detected in patients with RA (n = 59), which increased with age, unsurprisingly.[8] No associations were identified with other prognostic factors in RA, such as smoking status or seropositivity. More studies are needed to confirm these findings and to explore the potential role of CH in other systemic rheumatic disorders. Given the inflammatory cytokines and chemokines that

have been associated with CHIP, it could be hypothesized that these could result in autoimmune inflammatory syndromes, and further work in this area is much needed.

Autoimmune disorders and myeloid neoplasms

Autoimmune disorders are more commonly associated with myelodysplastic syndrome (MDS) and/or acute myeloid leukemia (AML). Most data regarding MNs in autoimmune disorders relate to RA and SLE. One large study in Sweden identified 42,262 hospitalized patients with RA followed over 24 years.[9] Of these, 52 patients developed AML over the course of the study period, with an overall increased risk ratio of 2.4 (95% confidence interval [CI], 1.79–3.15). Another large study using the Swedish Cancer registry stratifying patients into early RA (within 1 year of symptom onset) and advanced RA found 4 cases of AML in the former and 68 cases of AML in the latter group.[10] The standardized incidence ratio (SIR) was markedly increased in both groups (4.3 and 2.4 respectively). No cases of chronic myelogenous leukemia (CML) were noted in the early RA group, whereas 13 cases were seen in the advanced RA group with an SIR of 2.4 (95% CI, 1.3–4.1).

The associations between solid organ malignancies such as breast, cervical cancer, and non-Hodgkin lymphoma have been well described in the SLE literature. In contrast, the association of SLE with MNs has been assessed infrequently; the studies are limited and mostly observational. As such, it is hard to draw definitive conclusions regarding the cause of increased risks (underlying autoimmune disease, therapy, or unrelated contributors). A meta-analysis of 8 prospective lupus cohorts revealed an increased SIR of non-Hodgkin lymphoma, Hodgkin lymphoma, and leukemias (SIR of 2.3). There was no change after adjusting for age, sex, or location.[11] Two of these studies reported SIR of myeloid leukemia in patients with SLE of 3.4 (95% CI, 2.2–5.1). One group observed a large number of patients with SLE in California (n = 30,478); 29 cases of myeloid leukemia were noted, with an SIR of 2.96 (95% CI, 1.99–4.26).[12] A limitation of these studies is that they did not specify whether the leukemias were acute or chronic and sometimes did not differentiate between myeloid and lymphoid leukemias.

Although visceral malignancies have been clearly linked with SSc, there is little description of the interplay with MNs. A literature review (60-year duration) revealed 130 cases of hematologic malignancies, including leukemia (28 total, 2 cases of AML) and myeloproliferative disorders (11 cases of CML, 4 cases of myelofibrosis, and 1 case of polycythemia rubra vera).[13] However, these studies are difficult to interpret given the use of immunosuppressive agents and disease-modifying biologic therapies, which inherently increase the risk of neoplasms.

Autoimmune disorders occurring concurrently or after diagnosis of myeloid neoplasms

One of the most intriguing questions for hematologists and rheumatologists alike is the chicken-or-egg causality dilemma regarding the development of autoimmune disorders in patients with MNs: does autoimmune disorder predispose to MNs, do autoimmune disorders develop in these patients secondary to the neoplasm, or is the relationship bidirectional?

It has been well described in the literature that patients with MNs can present with concurrent or subsequent rheumatic manifestations. A wide range of rheumatic manifestations have been described in association with MDS, including inflammatory arthritis (eg, monoarthritis, polyarthritis, remitting seronegative symmetric synovitis with pitting edema syndrome), vasculitis (eg, polymyalgia rheumatica, relapsing polychondritis, and cutaneous vasculitis), and connective tissue disorders, including SS.

Approximately 10% to 25% of MDS cases are usually associated with rheumatic manifestations.[14,15]

The development of systemic vasculitis is limited to case reports and case series. One case series included a literature review that identified 55 cases in association with MDS, the most common of which was polyarteritis nodosa (PAN) (>25% of cases).[16] Absolute neutrophil count–associated vasculitis was rare in this series, which has been replicated in other small observational studies.

A nested case-control study using data from the United Kingdom (General Practice Research Database) identified 849 cases of MDS (either likely or possible) with approximately 4 times the number of matched controls. There was a marginally increased risk of MDS in patients with autoimmune disease (adjusted odds ratio [OR], 1.5; 95% CI, 1.1–2.0).[17] When stratifying by autoimmune disorder duration, a significantly increased adjusted OR of 2.1 (95% CI, 1.4–3.2) was noted for patients with long-standing autoimmune disease of greater than 10 years. This finding suggests that long-standing immune dysregulation has a major role in the pathogenesis of MNs.

Chronic myelomonocytic leukemia is an overlapping stem cell disorder with features of MDS and myeloproliferative neoplasms (MPNs); it also has a significant risk of transforming into acute leukemia. Definite autoimmune disease and systemic syndromes have been reported in this overlapping MN. A large study of 377 patients revealed that 20% had an autoimmune disorder.[18] Interestingly, in 58% of cases, these occurred before the diagnosis of chronic myelomonocytic leukemia (CMML) (a minority of autoimmune disorders were nonrheumatic: Hashimoto thyroiditis, myasthenia gravis, and granuloma annulare). Most responded to immunosuppression (77%) despite the heterogeneity of autoimmune disorder manifestations. Durable remissions were often seen with disease-specific interventions such as hypomethylating agents and allogenic stem cell transplant.

Autoimmune manifestations of CML include leukemic arthritis and bone pain. Leukemic arthritis can be symmetric or migratory polyarthritis and tends to be a manifestation of advanced disease.[19] It is less commonly seen in adult patients than in cases of pediatric leukemia; however, it can be challenging to manage and unresponsive to the usual immunosuppressants used to treat inflammatory arthritis/RA. The treatment of choice should be appropriate for the underlying leukemia.

In summary, there is a bidirectional association with several MNs and autoimmune disorders (**Table 1**). Given the temporal associations of MNs and autoimmune disorders and numerous confounding factors, large, well-designed, prospective studies are required to confirm these associations and guide therapeutic options.

Mechanisms of myeloid neoplasm in autoimmune disorders (pathogenesis and potential causes)

The pathogenesis of the development of MNs in autoimmune disorders remains convoluted and unclear. The heterogeneous nature of both groups contributes to this, along with difficulties establishing temporality. Understanding the mechanisms that drive these processes and the interplay between them is critical to determine the standard of care for screening, evaluation, and treatment of both disorders. **Fig. 1** provides a conceptual diagram.

Chronic immune stimulation Chronic inflammation as a risk factor for malignancy was first described in the nineteenth century by Virchow. More recent epidemiology studies have identified that chronic immune activation related to infections increases the risks of AML and MDS.[20]

Table 1
Summary of major autoimmune diseases that have been associated with myeloid neoplasms

Disease	Associations	Clinical Risks/Pearls
Autoimmune Disease		
Rheumatoid arthritis	AML, CML	—
SLE	AML, all MN	Lymphopenia increases risk: OR 14 (95% CI, 1.4–141)
MN		
MDS	Inflammatory arthritis, relapsing polychondritis, PMR, lupuslike syndrome, cutaneous vasculitis	—
CML	Carcinomatous polyarthritis	—
CMML	Rheumatoid arthritis, psoriasis, polymyalgia rheumatica, systemic vasculitis including PAN	—

Abbreviation: PMR, polymyalgia rheumatica.

A large project using data from the Surveillance, Epidemiology, and End Results (SEER) Medicare Assessment of Hematopoietic Malignancy Risk Traits (SMAHRT) study identified 13,486 cases of MNs, in which the presence of any autoimmune disorder was associated with an increased risk of AML with OR of 1.29 (95% CI,1.20–1.39). Statistically significant associations were detected for RA, SS, SLE, polymyalgia rheumatica, and PAN with MDS.[21]

Immune dysfunction has been implicated in the pathogenesis of many autoimmune disorders. One potential mediator is nuclear factor kB (NF-kB), which has been identified in MNs and autoimmune disorders. NF-kB regulates various aspects of the normal function of the innate and adaptive immune system.[22] It has been implicated in the pathogenesis of RA, inflammatory bowel disease (IBD), and atherosclerotic cardiovascular disease. Given the potential interplay between systemic autoimmune diseases and MNs, a potential role for NF-kB needs further exploration.

Genetic contributors The role of cytogenetic and molecular factors predisposing patients with autoimmune disorder to MN is still under investigation. Given common abnormalities between the 2 classes of disorders, some hypotheses can be made. These hypotheses include the role of *TP53* tumor suppressor genes (discussed later), the mammalian target of rapamycin pathway, and the role of human leukocyte antigen (HLA).

Data from the 1950s to 1980s highlight an increased risk of leukemia in patients with ankylosing spondylitis (AS). This increased risk was attributed at the time to radium exposure, which was used for management of AS in the prebiologic era.[23] The role of HLA-B27 in AS and other spondyloarthropathies, through interaction of the major histocompatibility complex with malignancy and spondyloarthritis, has not been well defined. It was investigated in a large study in Hong Kong: 59 carriers of HLA-B27 were identified to have a malignant hematologic disorder, 4 of whom had lymphoid malignancy. No case of MN was found.[24]

In mouse models, HLA class II genes have been associated with hematologic malignancy.[25] Although HLA-B27 has been established to be important in the heritability of AS,[26] a larger multicenter and multiethnic study by the Prospective Study of Outcomes in Ankylosing Spondylitis (PSOAS) cohort group highlighted potential roles of

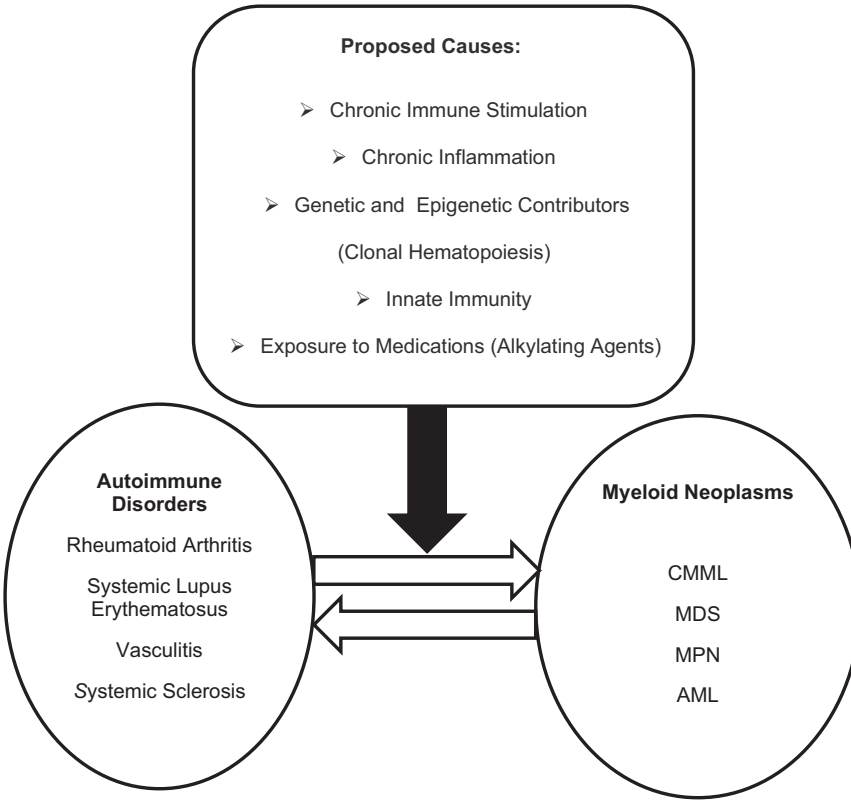

Fig. 1. Proposed mechanistic interplay between autoimmune disorders and MNs. AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms. (*Adapted from* Boddu PC, Zeidan AM. Myeloid disorders after autoimmune disease. *Ther-Relat Acute Leuk*. 2019;32(1):74-88; with permission.)

non-B27 class I HLA and also class II HLA in AS.[27] A study of HLA class 2 in patients with AS with malignancies has not been performed to the best of our knowledge and may be of benefit.

Innate immune system The role of interleukin (IL)-1 and *NLRP3* (nucleotide-binding domain–like receptor protein 3) in autoinflammatory disorders such as periodic fever syndromes is well established. Increased IL-1 levels have also been found in tissues of patients with autoimmune disorders inclusive of RA.[28] IL-1 has also been shown to play a role in the development of hematologic malignancy, including MNs.

The NLRP3 inflammasome (after upregulation by the *NF-kB* pathway) acts by downstream activation of IL-1 beta and IL-18, both of which are proinflammatory cytokines. Mouse models have identified a role of the inflammasome in RA, SLE, and even spondyloarthropathies (eg, AS).[29] The role of NLRP3 in the pathophysiology of malignancy and the role of other inflammasome complexes are still being determined. Note that activation of *NLRP3* has been associated with different cancer cell types, including melanoma and colon cancer. *NLRP3* has been proved to drive cell death through overexpression of proinflammatory pathways leading to increased apoptosis in

MDS.[30] Germline *MEFV1* mutations lead to the most common autoinflammatory/periodic fever syndrome, familial Mediterranean fever.[31] Interestingly, somatic mutations in the *MEFV* gene have been identified in a couple of patients with MDS who also presented with periodic fevers and cutaneous manifestations suggestive of Sweet syndrome.[32]

Therapy-associated myeloid neoplasms The medications used by rheumatologists to treat autoimmune disorders include antimetabolite medications (methotrexate, azathioprine, and mycophenolate mofetil), alkylating agents (cyclophosphamide), and biologic agents (tumor necrosis factor inhibitors [TNFi] and most recently non–tumor necrosis factor [TNF] biologics). Therapy-related MNs (t-MNs) have been well described with alkylating agents as well as DNA-topoisomerase agents (which are not commonly used in rheumatology practice). The risk of hematologic malignancy with antimetabolites has been considered lower historically, although there are newer data describing cases.[33]

Proposed causes for t-MNs include therapy-induced mutation to DNA damage sensing or repair genes (TP53), chromosome deletions with alkylating agents (chromosome 5 and 7 deletions),[34] and polymorphisms in genes that affect drug metabolism or transport.[35]

Somatic Mutations Associated with Myeloid Neoplasms and Autoimmune Disease

Common CHIP-associated mutations include *DNMT3A*, *TET2*, and *ASXL1*.[5] The *DNMT3A* gene is located at 2p23 and serves as one of the genes that encodes DNA methyltransferase enzymes, which play a role in methylation of CpG dinucleotides.[36] Mutations of this gene have been noted in a significant subset of patients with MDS and AML.[37]

TET2 encodes proteins that play a role in the control of DNA expression through demethylation.[38] *TET2* mutations are common in MNs, especially CMML.[39] *TET2* has also been reported to potentially participate in regulation of both the adaptive (T-helper [Th] 1 and Th17 cells) and innate immune systems.

The *ASXL1* (additional sex combs–like 1) gene regulates epigenetic marks and transcription through the polycomb repressor complex, with mutations being uniformly deleterious across MNs.[40–42]

Abnormal DNA methylation has been shown in several epigenetic studies of autoimmune disorders inclusive of RA, SLE, and SS.[31] A clear interaction between DNMT3A mutations and autoimmune disease has yet to be proved.

Other genes commonly associated with CHIP include *JAK2* and *TP53*. *JAK2* is a common driver mutation in MPNs and has been associated with leukocytosis, thrombocytosis, and thrombotic complications.[35] *TP53* somatic mutations are usually seen in the context of therapy-related MNs and are associated with very poor outcomes.[37]

The primary driver of progression from CHIP to an overt myeloid neoplasia is not completely understood, but the combination of inflammation and aging is thought to play a major role.[43]

Various reasons for the development of these somatic mutations have been identified, including environmental mutagens (radiation, cigarette smoke, air pollutants), mutagenic drugs (chemotherapeutic agents)[36] or impaired DNA repair, and altered telomere dynamics associated with aging.[31,41,44]

The data exploring these mutations in autoimmune and rheumatic disease are limited and the mechanisms are yet to be fully defined. However, *TP53* mutations have been extensively studied in mouse models; *TP53*-deficient mice are more likely to develop inflammatory arthritis.[45–47]

The 1 study that assessed CH in patients with RA along with aplastic anemia and healthy controls[8] identified *DNMT3A* mutations to be the most common (n = 4), followed by *TET2* (n = 3). None of these patients had MN or cancer. Interestingly, 1 patient with RA had a *TP53* mutation (17:g.7574003G>A), which was associated with cervical cancer requiring surgical intervention (unclear from data whether this was a somatic or germline mutation). Further studies are needed to assess whether chronic inflammation from autoimmunity favors the development of CHIP and subsequent MNs, or whether CHIP and MNs result in inflammation and autoimmunity.

Myeloid Sequelae of Rheumatologic Therapies/Medications

The determination and quantification of the risk of malignancy with DMARDs and biologic agents in rheumatic disease is extremely difficult. The overall burden of malignancy unrelated to rheumatic disease is high in the general population. Moreover, the risk of malignancy conferred by specific rheumatic diseases and the use of immunosuppressive agents, some of which are well known to have neoplastic potential, further complicates risk assessment. Given the broadness of this topic and matters discussed earlier, this article focuses on the myeloid sequelae of commonly used agents by rheumatologists. t-MNs comprise the spectrum of disorders that were discussed previously in the setting of chemotherapeutic, disease-modifying agents or other exposures such as radiation. This group can be divided into therapy-related AML, therapy-related MDS (t-MDS), and t-MDS/MPN. T-MNs are often characterized by specific cytogenetic changes, especially when they occur in the context of alkylator-based therapies.

Traditional immunosuppressive agents/disease-modifying antirheumatic drugs

The following commonly used immunosuppressive agents are discussed here: cyclophosphamide, azathioprine, methotrexate, and TNFi.

Cyclophosphamide Cyclophosphamide (CYC) has been long been attributed with significant risk of malignancy inclusive of lymphoma, leukemia, and visceral malignancies such as bladder cancer.[1] In light of these side effects and the development of multiple immunosuppressants within the last 2 decades, clinical use of CYC is now restricted to severe manifestations of rheumatic disease, such as diffuse alveolar hemorrhage, central nervous system vasculitis, and refractory renal involvement in SLE.[48–50] In addition, dose adjustments/reductions (eg, for the EuroLupus regimen for lupus nephritis) as well as intermittent intravenous administration rather than daily oral dosing of cyclophosphamide has become more common.[51] This trend is supported by noninferiority in clinical studies as well as reduction in adverse events.[52]

There have been clear links between cyclophosphamide usage and MNs (including MDS and CML). It typically takes 5 to 7 years after exposure to alkylating agents before t-MNs develop.[53,54] MDS is most common, with further clonal evolution to AML. Common karyotypic changes include deletions of chromosome 5 and/or 7 (7q/-7 and 7q/-5).[55]

There are some studies evaluating the role of CYC in t-MNs in specific autoimmune disorders. In patients with Granulomatosis with polyangiitis (GPA), approximately 8% of patients treated with CYC for remission induction and maintenance therapy developed MDS.[56] The rate was almost doubled with a high cumulative dose (>100 g). Multiple studies have identified an increased risk of both solid organ and hematologic malignancy in SLE, although this has been found to be independent of CYC use.[57,44]

The risk of hematologic malignancy is increased in patients with RA treated with cyclophosphamide[58] (**Table 2**). With the advent of many newer agents for RA in the

last 10 to 20 years with favorable side effect profiles, cyclophosphamide has fallen out of use in the management of RA. In very rare and refractory cases (RA vasculitis or RA-associated large granular lymphocyte (LGL) leukemia), there may still be a role for cyclophosphamide. Clinicians deciding to initiate CYC in this subset of patients with RA should weigh this risk-benefit profile in addition to consideration of any alternate options.

Azathioprine Azathioprine is used to treat a wide spectrum of autoimmune disorders. Multiple studies have consistently shown an increased risk of lymphoproliferative disorders in patients with RA.[49] Although there was concern that this was related directly to the antimetabolite, a more recent systematic review revealed that the approximately 2-fold increase in lymphoma incidence in RA is related to the underlying disorder (severity and disease duration) and not the therapeutic agents (azathioprine and methotrexate).[33] This finding highlights the challenges in studying the complex multidirectional interplay between autoimmunity, malignancy, and immunosuppressive agents.

A Medline search in 2010 identified 56 cases of azathioprine-associated MDS and AML,[59] confirming the association of azathioprine with MNs. However, 52% of these cases were organ transplant recipients, and a markedly increased risk of solid organ, skin, and hematologic malignancies has been shown in organ transplant recipients. This increased risk may be related to higher doses of azathioprine in transplant patients in the setting of additional risk factors. The remainder of cases identified by Kwong[59] had autoimmune disorders; most of these were related to abnormalities in chromosome 7. In approximately 20% of the cases, recurrent cytopenias preceded t-MDS/AML, and this may be 1 indicator to follow for patients on azathioprine.

Focusing specifically on MNs, data were limited to case reports, and case series have been reported in RA, SLE, and IBD. However, a large case-control series[60] (see **Table 2**) identified a 7-fold increased risk of MN (AML or MDS) in patients with a primary autoimmune disease. Another case-control study found no association between azathioprine and MN, although the number of cases was small, which may have affected outcomes.[61]

Methotrexate Methotrexate is one of the most commonly used medications in rheumatology. It has been clearly shown to cause myelosuppression and lymphoproliferative disorders. The role of methotrexate in causing therapy-associated myeloid neoplasia is far from clear. The limited studies performed have found no association between methotrexate and myeloid neoplasia in RA.[62,63]

Biologic therapies (tumor necrosis factor inhibitors) TNFi are widely used for management of many rheumatic disorders, including RA, AS, and psoriatic arthritis. Safety data were initially accumulated during various clinical trials with subsequent population-based studies and through use of claims databases. Most of the studies have assessed the links of lymphomas and solid organ malignancies with TNFi.

The number of studies assessing MNs in patients with definite autoimmune disease is limited (**Table 3**). In a large Swedish cohort study of patients with RA divided into 3 groups (early RA/incident cohort, prevalent cohort/established RA and RA receiving TNFi), there was no significant increase in MPNs or hematologic malignancies in general in the group receiving a TNFi[10] (SIR 0 for AML and CML). Another large cohort study assessing TNFi use for RA in North America revealed a numerically significant hazard ratio of hematologic malignancy but the results were statistically insignificant.[64]

The large study by Ertz-Archambault and colleagues[60] identified 13 (15.1%) patients with MN who received a TNFi for autoimmune disease compared with 33 (19.2%)

Table 2
Selection of studies exploring the effects of select disease-modifying antirheumatic drug therapies and risk of myeloid neoplasms in autoimmune diseases

Medication	Author, Year	Study Design	Methods	Results	Conclusion
(1) Cyclophosphamide	Bernatsky et al,[62] 2008	Case control	Administrative database, 23,810 patients with RA	Adjusted rate ratio of hematologic malignancy: 1.84; 95% CI, 1.24–2.73	Increased risk of hematologic malignancy, cyclophosphamide exposure
	Baker et al,[67] 1987	Case control	Single-center US practice, patients with RA,119 cyclophosphamide and 119 controls	37 malignancies in the CYC arm, only 2 leukemias noted (subtype not stated)	Although there is in an increased risk of malignancy in CYC group, unable to conclude whether there is an increased risk of MN
(2) AZA	Bernatsky et al,[62] 2008	Case control	Administrative database, 23,810 patients with RA	Adjusted rate ratio of hematologic malignancy: 1.07; 95% CI, 0.74–1.54	No increased risk with Imuran exposure in this RA population
	Ertz-Archambault et al,[60] 2017	Case control	40,011 patients with a primary autoimmune disease, identified patients with concomitant MDS or AML and compared with controls (2 controls per case)	86 patients had either AML or MDS. OR of AZA: 7.05; 95% CI, 2.35–21.13	AZA exposure associated with a 7-fold risk of MN
	Lofstrom et al,[61] 2009	Nested case control	6438 SLE cases, 8 confirmed cases of SLE with myeloid leukemia	AZA: 0.8 (95% CI, 0.1–4.1)	AZA was not a cause of myeloid leukemia in SLE population
(3) Methotrexate	Bernatsky et al,[62] 2008	Case control	Administrative database, 23,810 patients with RA	Adjusted rate ratio of hematologic malignancy: 1.12; 95% CI, 0.93–1.34	MTX was not associated with an increased risk of MN

Abbreviations: AZA, azathioprine; MTX, methotrexate.
Data from Refs.[33,51,55,56]

Table 3
Studies exploring the effects of tumor necrosis factor inhibitors and risk of myeloid neoplasms in rheumatoid arthritis

Medication	Author, Year	Study Design	Methods	Results	Conclusion
TNFi	Setouguchi et al,[64] 2006	Cohort (using 3 health care databases)	Pooled cohort of patients with RA (2 US patients and 1 Canadian), 1152 received TNFi and 7306 MTX	11 hematologic malignancies, adjusted HR, 1.37; 95% CI, 0.71–2.65	No increased risk of hematologic malignancy in TNF-treated group compared with MTX
TNFi	Askling et al,[10] 2005	Population-based cohort study of RA	One prevalent cohort, 1 incident cohort, and 1 cohort of TNFi-treated patients (n = 4160)	11 hematopoietic malignancies (1999–2003), only 2 undefined leukemias. No cases of AML, CML, or PRV	No increased risk of MN in patients with RA treated with TNFi

Abbreviations: HR, hazard ratio; PRV, polycythemia rubra vera.

Data from Askling J, Fored CM, Baecklund E, et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. *Ann Rheum Dis*. 2005;64(10):1414-1420; and Tarr T, Gyorfy B, Szekanecz É, et al. Occurrence of Malignancies in Hungarian Patients with Systemic Lupus Erythematosus. *Ann N Y Acad Sci*. 2007;1108(1):76-82.

controls. An unadjusted OR of 0.71 (0.33–1.53) was detected; therefore, they concluded that there was no increased risk of MN with TNFi. Given that TNFi are recommended for patients with refractory inflammatory arthritides (RA, spondyloarthritis)[65,66] and are among the most frequently prescribed medications, these findings are reassuring, but they do need ongoing scrutiny.

SUMMARY

There is an increased risk of MNs in autoimmune disease. This risk is independent of other risk factors, such as smoking and immunosuppressive therapy. There are certain genetic predispositions, including somatic mutations, which may account for some of the risk and warrant further investigation. The strongest evidence for t-MN exist for cyclophosphamide, although recent studies have also identified azathioprine as a potential offending agent. Although larger studies are needed to reproduce these findings, these risks should be considered when deciding on immunosuppression for rheumatic disorders, especially in individuals with additional risk factors for malignancy.

CLINICS CARE POINTS

- Clonal hematopoiesis (CH) is associated with chronic inflammation, endothelial dysfunction and increased all-cause mortality. CH may be linked to autoimmune disease which warrants further exploration.
- Autoimmune diseases (AD) have been associated with an increased risk of myeloid neoplasms. The greatest risk is seen in RA and SLE patients though evidence of an association between MN and other AD's (vasculitis, sjogren's syndrome) has been identified in small observational studies.
- Myeloid neoplasms (MN) can present with features of concurrent or subsequent autoimmune diseases/systemic inflammatory syndromes.
- Therapy-associated myeloid neoplasms can develop as a delayed effect of treating an underlying autoimmune disorder. The strongest evidence exists for Cyclophosphamide and Azathioprine.
- More data evaluating the risks of MN with biologic agents is needed.

DISCLOSURE

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