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When inflammatory stressors dramatically change, disease phenotypes may transform between autoimmune hematopoietic failure and myeloid neoplasms

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Aplastic anemia (AA) and hypoplastic myelodysplastic syndrome are paradigms of autoimmune hematopoietic failure (AHF). Myelodysplastic syndrome and acute myeloid leukemia are unequivocal myeloid neoplasms (MNs). Currently, AA is also known to be a clonal hematological disease. Genetic aberrations typically observed in MNs are detected in approximately one-third of AA patients. In AA patients harboring MN-related genetic aberrations, a poor response to immunosuppressive therapy (IST) and an increased risk of transformation to MNs occurring either naturally or after IST are predicted. Approximately 10%–15% of patients with severe AA transform the disease phenotype to MNs following IST, and in some patients, leukemic transformation emerges during or shortly after IST. Phenotypic transformations between AHF and MNs can occur reciprocally. A fraction of advanced MN patients experience an aplastic crisis during which leukemic blasts are repressed. The switch that shapes the disease phenotype is a change in the strength of extramedullary inflammation. Both AHF and MNs have an immune-active bone marrow (BM) environment (BME). In AHF patients, an inflamed BME can be evoked by infiltrated immune cells targeting neoplastic molecules, which contributes to the BM-specific autoimmune impairment. Autoimmune responses in AHF may represent an antileukemic mechanism, and inflammatory stressors strengthen antileukemic immunity, at least in a significant proportion of patients who have MN-related genetic aberrations. During active inflammatory episodes, normal and leukemic hematopoieses are suppressed, which leads to the occurrence of aplastic cytopenia and leukemic cell regression. The successful treatment of underlying infections mitigates inflammatory stress-related antileukemic activities and promotes the penetration of leukemic hematopoiesis. The effect of IST is similar

to that of treating underlying infections. Investigating inflammatory stress-powered antileukemic immunity is highly important in theoretical studies and clinical practice, especially given the wide application of immune-activating agents and immune checkpoint inhibitors in the treatment of hematological neoplasms.

KEYWORDS

aplastic anemia, myelodysplastic syndrome, acute myeloid leukemia, inflammatory stressors, leukemic transformation, antileukemic immunity

General overview of aplastic anemia and myeloid neoplasms

Aplastic anemia (AA) is an acquired form of autoimmune hematopoietic failure (AHF). Traditionally, AA has been considered a benign hematological disease. AA pathogenesis results from the destruction of hematopoietic progenitor cells (HPCs) by deranged autoimmune responses that occur mainly in the bone marrow (BM) environment (BME). After an initial insult by pathogenic environmental challenges, such as genotoxic exposure or microbial infection, the activated immune responses perpetuate and result in immune-mediated impairment of blood cell production and subsequent clinical presentations of BM hypoplasia/aplasia and peripheral cytopenia in one or more cell lineages (1, 2). Currently, the diagnosis of AA is largely based on markedly decreased BM cellularity and hematopoietic volume with fatty replacement and the absence of overt dysplastic hematopoiesis in HPCs (3, 4). AA is a highly heterogeneous disease entity that converges on a pathophysiological process of persistently deranged autoimmune responses and heavily exhausted HPCs. Patients with AA exhibit varying clinical presentations regarding disease phenotype, disease severity, disease course, treatment response to immune suppressants, and the likelihood of transformation to myeloid neoplasms (MNs). This high heterogeneity is driven by the diversity of the constitutional genetic background, the competence of innate immune cells, the appropriateness of adaptive immune responses to environmental challenges, basic functions of other organ systems, events that guide immune responses, and perhaps most importantly, conditions that sustain deranged autoimmune reactions (1–4).

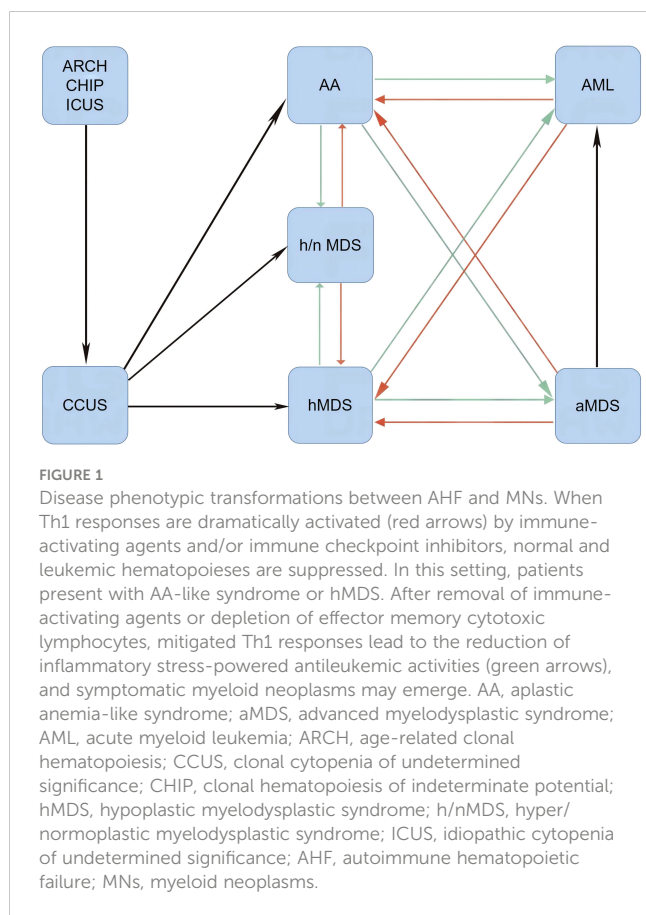
Myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), and acute myeloid leukemia (AML) are unequivocal MNs. MNs result from the acquisition and accumulation of somatic mutations in HPCs. Genetic damage is generated from the exposure of HPCs to various oncogenic agents, and the emergence of leukemic clones arises from the selective advantage of transformed HPCs in the context of chronic inflammatory BME. Oncogenic mutations in transformed HPCs lead to altered proliferation, self-renewal, and antiapoptotic

capacity. The dysregulated growth of leukemic cells results in the overgrowth of their normal counterparts and the suppression of normal blood cell production, clonal hematopoiesis, and corresponding hematological presentations (5–8). The presence of dysplastic features indicates a diagnosis of MNs, and an increased percentage of myeloblasts is the most significant biomarker representing leukemic hematopoiesis and entry into advanced stages (9, 10). Immunological, cytogenetic, and biological molecular analyses can provide valuable information for diagnosis, classification, and risk stratification. MDS, MPN, and AML are also highly heterogeneous with somatic mutations involving hundreds of genes in association with their pathogenesis. Each somatic mutation plays a distinctive role in malignant transformation or affects clinical complications, hematological presentations, cellular components, immunological signatures, disease progression, and treatment response (5–8).

Accumulating evidence supports that there is an intrinsic relationship between AHF and MNs regarding their clonal hematopoiesis, immunological profile, and disease phenotypic transformations.

Reciprocal transformations between AA and MNs

By definition, AA is distinct from MDS, MPN, and AML with differences in fundamental pathogenesis, biological behaviors, laboratory features, treatment strategies, and prognostic significance. However, disease phenotypes can transform between AHF and MNs. The natural transformation of AA to MNs has been widely investigated (11–14) and is generally ascribed to the acquisition and accumulation of oncogenic mutations due to selective pressure and immune exhaustion in the setting of a chronic inflammatory milieu (15–18). It is well known that antithymocyte globulin (ATG) plus cyclosporine-based immunosuppressive therapy (IST) promotes leukemic transformation. Approximately 10%–15% of patients with severe aplastic anemia (SAA) experience leukemic transformation following IST, and in some patients, this transformation emerges



during or shortly after IST (19–23). Such a short interval that spans the transformation process indicates that leukemic clones preexist in the SAA stage (24–27) and rapidly expand due to depletion of cytotoxic T lymphocytes (CTLs) or the induction of immune tolerance (28–32) rather than due to the acquisition of novel molecular events. In patients with genetic aberrations typically observed in MNs, there is a greater frequency of transformation to MNs. Moreover, 20%–30% of SAA patients fail to respond to IST, and these patients have a significantly greater frequency of MN-related genetic aberrations compared to patients who achieve a good treatment response. Even in patients who achieve a hematological response, the presence of MN-related genetic aberrations is associated with a reduced sensitivity to IST, a low rate of deep remission, a high frequency of disease relapse, and a significantly increased risk of leukemic transformation (19–23).

Leukemic transformation in SAA patients can also occur after successful treatment of underlying infections and is frequently separated by a short duration of hematological remission. A rapid increase in leukemic blasts is the representative presentation of leukemic hematopoiesis (33–35). Moreover, patients with definitively diagnosed MNs can develop an aplastic crisis during infectious episodes. During aplastic crisis, the cytological and immunological features resemble those of SAA with a regression of leukemic blasts (35, 36). It remains unclear why patients with a similar genetic landscape or even an identical genetic background exhibit variable disease phenotypes. Furthermore, the significance

of disease phenotypic transformations has not been fully elucidated through basic research and clinical practice. It is possible that environmental factors, most likely changes in inflammation strength or depletion of effector immune cells, affect the disease phenotype and contribute to phenotypic transformations (as schematized in Figure 1).

Clonal hematopoiesis in AA

With the wide application of next-generation sequencing (NGS) in the diagnosis, mutational analysis, and risk stratification of hematological diseases (37, 38), it has been shown that more than one-third of patients definitively diagnosed with AA carry genetic aberrations that are well-known driver mutations in MNs (19–27). Although the number and clone size of mutant genes in AA are much smaller than those in MDS and AML, the number and clone size of these mutant genes can increase in patients who respond to IST (20–22). Currently, AA is also known to be a clonal hematological disease. Clonal HPCs gain a selective proliferative and survival advantage over their normal counterparts in a chronic inflammatory setting and become the dominant hematopoietic components (24–27). Moreover, some patients with MDS or AML can present heavily reduced BM cellularity at initial diagnosis or during disease progression, and patients with low-risk MDS have an immunological landscape similar to that of SAA (39–43).

Immune dysregulation and an inflamed BME in AHF

AA and hypoplastic MDS (hMDS) are typical forms of immune-mediated AHF, and they share similar cytological and immunological landscapes (39, 40). In AHF, autoimmune CTLs (43–45) and natural killer (NK)/NKT cells (46–48) become activated and expanded. Trained CTLs [effector memory CTLs (emCTLs)] and NK/NKT cells (effector memory NK/NKT cells) exhibit elevated killing activities (43–48), increased secretory capacities (49–51), and enhanced sensitivities to antigen stimulation (52, 53). The oligoclonal feature of expanded emCTL infiltrating the BM suggests the presence of chronic stimulation that is driven by an antigen from the BME (43, 50). The excessive production of hematopoietic inhibitory mediators (54–57) due to T helper type 1 (Th1) immune responses (58–60) plays a central role in AHF pathogenesis. Additionally, upregulated expression of proapoptotic molecules (61–63) and decreased telomerase activity (64, 65) accelerate the death of HPCs. Upregulated expression of Toll-like receptors (TLRs) and costimulatory molecules in response to chronic inflammation enhances sensitivity to antigen stimulation, propagates inflammatory responses, induces the production of reactive oxygen species, augments apoptotic signals, amplifies pyroptotic cell death, and favors a selective survival advantage, which forms a positive feedback loop to cause ineffective hematopoiesis and sustain clonal proliferation (66–69). Moreover,

the number and function of regulatory T cells (Tregs) and regulatory B cells (Bregs) are dramatically decreased (70–73), as is the downregulation of anti-inflammatory mediators (74–76). Defects in HPCs and dysregulation of immune responses are also present in complete remission following IST (77, 78). Autoimmunity targeting HPCs by autoantigen-specific lymphocytes (50, 59) attracts a variety of immune cells (79–81). Immune cell infiltration and activation create an immune-active BME (79–83), which forms an inflammatory background and may determine a BM-predominant autoimmune impairment (39–42). The BM-predominant autoimmunity is amplified by an additional antigenic stimulation (84–87). Th1 immune responses suppress the production of erythrocytes, granulocytes, platelets, and B lymphocytes (49, 55–57, 87), which results in clinical and laboratory features of AA and hMDS (3, 4, 9, 10).

The development of an immune-active BME can be achieved in several ways. 1) Pattern recognition receptors (PRRs) sense pathogen-associated molecular patterns (PAMPs), or antigen-specific CTLs target pathogenic antigens of microbes that can survive and smolder in BM cells (84–87). 2) Cellular components that cross-react with microbial epitopes are targeted by autoimmune lymphocytes trained in active infectious diseases (88), particularly inflammatory conditions involving the gastrointestinal tract (89, 90), which can continuously supply intestine-derived antigens from pathogenic or commensal microbes in the context of increased epithelial permeability (90–92). 3) Somatic mutations in epigenetic modulators or transcription factors lead to the excessive production of inflammatory cytokines (93, 94). 4) PRRs sense damage-associated molecular patterns (DAMPs) (95–98), or autoimmune CTLs target neoplastic antigens of genetic or epigenetic products (40, 59, 99–101) in transformed HPCs. If autoimmune responses target DAMPs or neoplastic antigens on leukemic HPCs, the role of autoimmune responses in AHF may be antileukemic (95, 97, 102).

Contribution of inflammatory stressors to autoimmune diseases

Chronic intracellular infections in AID pathogenesis

Chronic infectious diseases, especially intracellular infections, are closely associated with the development, persistence, and acceleration of autoimmune-related impairments in various organ systems (103–110). Autoimmune diseases (AIDs), which usually manifest as organ-specific impairments, are frequently localized at sites away from infectious niduses. The severity of AIDs commonly parallels the severity of chronic infectious conditions (111, 112), which provides persuasive evidence that chronic infections contribute to the perpetuation and acceleration of autoimmune responses. Low-affinity autoimmune lymphocytes can escape the process of clonal selection and clonal deletion (113–116), and the

development of AIDs critically requires the engagement of environmental factors to disturb immune homeostasis and generate high-affinity autoimmune lymphocytes by somatic mutations in the antigen-binding region (affinity mutation) (117–119).

Mechanisms by which infectious diseases induce AID pathogenesis

Several hypotheses have been proposed to explain the relationship between the occurrence of infectious diseases and the generation of autoimmune responses. 1) When infected by microbes or inoculated with vaccines, hosts generate high-affinity antibodies or emCTLs through class switching and affinity maturation in the fight against invading pathogens. High-affinity antibodies or emCTLs cross-react with epitopes of autoantigens in certain tissues (molecular mimicry) (120–123). After being trained in response to microbial infections, these autoreactive lymphocytes migrate to remote organs, exert an immunological attack, and induce tissue damage when recognizing cognate autoantigens (117–119). 2) When tissue is infected by pathogenic microbes, autoreactive lymphocytes in the inflamed niche can be activated and trained by antigen-presenting cells and autoantigens, which form high-affinity autoimmune B and T cells and exert an immunological attack on corresponding tissues (bystander activation) (124–126). 3) In the inflamed niche, cryptic epitopes can be exposed, recognized, and presented to immune cells as exotic antigens to elicit immunological reactions. This immunological attack on cryptic epitopes sustains inflammatory impairment in affected tissues (epitope spreading) (127, 128). 4) During chronic infections, antigens or antibodies can be modified, frequently by glycosylation, which results in altered antigenicity of tissue components or an altered affinity of autoantibodies (posttranslational modifications) (129–132). 5) Certain components of infecting microbes can activate polyclonal lymphocytes and result in the generation of self-reactive antibodies and autoimmune CTLs that can bind to tissue components. These microbial components are called superantigens. Superantigen-induced self-reactive antibodies or autoimmune CTLs initiate an immunological attack (superantigen stimulation) (133–135). The same microbes can trigger AIDs in different organ systems through different mechanisms, and AIDs in certain organs can be induced by different microbial infections through different mechanisms.

After pathogenic antigens have been cleared, the host immune system rapidly returns to a homeostatic state by complex immune regulatory mechanisms to limit inflammatory damage (136–138). However, effector memory lymphocytes have the ability to respond promptly and play a major role when the host encounters the same or cognate epitopes (139–141). Chronic infectious diseases can continuously supply pathogenic antigens or create an inflammatory milieu in which host immune cells persistently produce inflammatory cytokines (84–92) and thereby synergistically sustain the activated form of host autoimmune cells in cognate antigen-dependent or antigen-independent pathways (139–141) to attack antigen-specific cells and innocent bystander tissues (142, 143).

Gut inflammatory conditions in AID pathogenesis

In addition to chronic intracellular infections, the gastrointestinal tract is another common chronic inflammatory nidus. As an important organoid in the human body (144, 145), the gut microbiota plays an essential role in the stimulation, education, and maturation of the host immune system and is the most important element that dynamically affects host immune homeostasis throughout life (146–148). Indeed, host peripheral lymphatic tissues develop poorly in the absence of the gut microbiome (149–151). The associations of AIDs with gut dysbiosis and gut inflammatory conditions have been investigated extensively (90, 92, 147, 152, 153). Patients with inflammatory bowel disease (IBD) have a high frequency of extraintestinal autoimmune manifestations including systemic connective tissue diseases, seronegative spondyloarthritis, systemic vasculitis, and organ-specific autoimmunity in different organ systems (154, 155).

The critical requirement of the gut microbiome for inducing and sustaining autoimmunity in genetically susceptible animal models has been verified in multiple AIDs and provides affirmative evidence for the contribution of gut dysbiosis and gut inflammatory disorders to the development of autoimmune pathogenesis. These animal models spontaneously develop AIDs under conventionally reared conditions, but autoimmune impairment does not occur in germ-free or specific pathogen-free conditions (155–161). In animal models of AIDs, the clearance of the gut microbiome can effectively alleviate disease severity (157). Even in conventionally reared animals, administration of probiotic antibiotic agents can significantly delay disease penetration (162). This is not surprising because the gastrointestinal tract harbors the most abundant lymphoid tissues and microbial community (163, 164). The microbial community and gut homeostasis are constantly subject to various environmental challenges (165, 166), including pathogen intruders (167–170), chemical damage (171, 172), drug exposure (173–175), and nutrient delivery (176–178). Harmful challenges can compromise the integrity of the intestinal epithelium, induce dysfunction, cause dysbiosis, and trigger gut inflammatory disorders; these can occur not only by injuring diseased segments but also by affecting other segments through disruption of microbial ecology (179–181). Gut dysbiosis can initiate immune responses and cause inflammatory lesions in the gastrointestinal tract (181–184). In the setting of a compromised intestinal structure, impaired barrier functions allow host immune cells to come into intimate contact with intestine-derived antigens (89–92). This occurs not only from pathogenic agents but also from commensal microbes and undigested food (185–187) and thereby activates host immune cells, disturbs immune homeostasis, overrides immune tolerance, and triggers deranged immune responses (188–192).

The gastrointestinal tract can continuously supply a large amount of intestine-derived antigens and persistently activate a substantial number of immune cells. The structural and functional features of the gastrointestinal tract render the organoid vulnerable to be an active inflammatory nidus in which host immune

homeostasis is disturbed and inflammatory stresses are sustained with sufficient inflammation strength to perpetuate autoimmune responses in remote organ systems (163, 164). In this process, probiotic commensal microbe-derived metabolites play important roles in maintaining epithelial integrity, regulating host immune responses, and modulating autoimmunity (177, 178, 193–196). An inadequate dietary supply can induce gut dysbiosis and immune dysregulation and affect epithelial repair function (197–200). Chronic gut inflammatory disorders likely work as amplifiers linking systemic immune dysregulation with environmental factors to augment the intensity of extraintestinal autoimmune responses and thereby power autoimmune impairment (201–203). Gut microbiota also plays an indispensable role in combating intracellular infections (204–206) and in eliciting anti-infection responses through vaccine inoculation (207, 208), which reinforces the role of gut microbiota in amplifying systemic immune activities.

Non-specific antigen stimulation in AID pathogenesis

Autoimmune impairments in genetically predisposed animals can also be initiated by adjuvant agents, PAMPs, recombinant inflammatory cytokines, and immune checkpoint inhibitors (ICIs). The *Bacillus Calmette–Guerin* (BCG) vaccine has long been recognized in the induction of AIDs (209, 210), and Freund's adjuvant has been widely used in experimental models to trigger autoimmunity (211, 212). Autoimmune responses are common complications that occur following not only BCG but also other inoculations. This leads to the creation of the specific term “autoimmune syndrome induced by adjuvant (ASIA)” (213–216). Polyriboinosinic acid:polyribocytidylic acid (polyI:C) (217, 218), endotoxins (219–221), and fungal peptidoglycans (222–224) activate different PRRs. These PAMPs can trigger and sustain immune derangement by disrupting immune homeostasis (225, 226). ICIs (227, 228) and even hematopoietic growth factors (229, 230) can promote the penetration of AIDs. The initiation of AIDs by non-specific antigen stimulation suggests that systemic inflammatory stressors, rather than specific antigen stimulation, can synergize with a primary immune-active background to trigger deranged organ-specific autoimmune processes (125, 126, 139).

Potential antileukemic mechanism in AHF

In 2009, Nissen (231) proposed that autoimmune responses occurring in acquired AA may function as an antileukemic mechanism against malignant proliferation. In the SAA stage, the decreased number and function of Tregs and Bregs, the decreased production of inhibitory cytokines, the reduced expression of coinhibitory molecules, the increased Th1 responses, the increased number and function of CTLs and NK/NKT cells, the

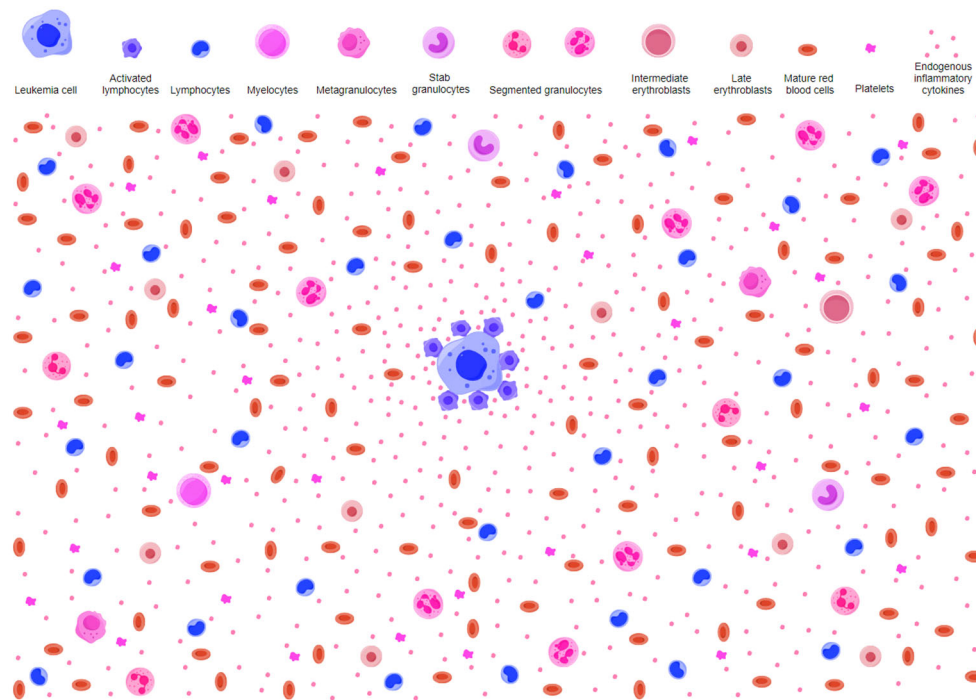


FIGURE 2

Potential antileukemic mechanism in AA-like syndrome. AA-like syndrome is characteristic of reduced HPCs and relatively increased lymphocytes without overt dysplasia. Early hematopoietic progenitors are rare. AA-like syndrome is caused by host immune surveillance against transformed HPCs. Immune responses to neoplastic molecules on leukemic HPCs activate innate and adaptive immune cells. Activated lymphocytes secrete proinflammatory cytokines and create an inflammatory background in the BME. Normal HPCs are suppressed by hematopoietic inhibitory mediators as innocent bystander victims in the process of host immune cells attacking leukemic HPCs. Because of the preferential suppressive effects on transformed HPCs, myeloblasts are hardly observed. The small number of nucleated hematopoietic cells and more intensive responses to transformed HPCs make it difficult to identify overt aplasia, which results in a diagnosis of AA in most circumstances. AA, aplastic anemia; HPCs, hematopoietic progenitor cells; BME, bone marrow environment.

increased antigen-presenting activities, and the excessive expression of proapoptotic and costimulatory molecules on HPCs may represent an adaptive process in response to ongoing antigen stimulation. Along with disease progression, the immunological signature in the BME is transformed from a Th1-predominant response to an immune exhaustion state in which the function of infiltrated autoimmune lymphocytes is inhibited and immune surveillance is gradually dampened in adaptation to the chronic inflammatory milieu. The immune exhaustion state favors leukemic cell survival and facilitates the penetration of symptomatic MNs (15–18). The extrapolation was mainly drawn from tumor regression and concomitant autoimmune phenomena in diseased organs during the treatment of non-hematological malignancies with immunological therapy. The author also described examples of hematological neoplasms in which leukemic cell regression was observed along with the appearance of prolonged aplastic cytopenia and autoimmune reactions (AA-like syndrome) after intensive chemotherapy or other treatment modalities. The author coined the phrase “pancytopenia of unknown significance” to describe this clinical phenomenon. Severe BM hypoplasia, systemic inflammatory symptoms, increased autoreactive CTLs, and decreased Tregs were observed in this AA-like syndrome. These cytological and immunological features indicate that antileukemic immunity has been reinvigorated.

Indeed, AHF can occur in response to neoplastic antigens or DAMPs (95, 96, 102, 232). The acquisition of autoantibodies against the neoplastic antigen carbonic anhydrase I induces AA-like syndrome and leukemic cell regression (102). Constitutive activation of the RAS-MAPK pathway can induce HPC senescence (96), and the absence of PRRs that sense neoplastic molecules results in accelerated leukemia cell proliferation (97). Similar to solid tumors (233–235), immune responses to neoplastic antigens (99–102) and stress in response to HPC damage (95–97) establish a chronic inflamed BME (93, 94, 236, 237). The inflamed BME enhances sensitivity to exogenous antigen stimulation (52, 66, 67) and accelerates apoptotic death in leukemic (95, 96, 238, 239) and normal (95, 96, 142, 143) HPCs, which are the common clinical and laboratory features of AA and low-risk MDS (39, 40, 49, 240) (as schematized in Figure 2).

Antileukemic immunity-induced Th1 responses preferentially repress leukemic cells and their normal counterparts, which can lead to pronounced neutropenia (42, 102, 232). Autoimmune neutropenia can persist for many years prior to the emergence of symptomatic MNs. In this stage, the BM is hypocellular, and cytological and immunological features exhibit immune-mediated hematopoietic impairments in the absence of morphologically identifiable leukemic blasts (241, 242). A significant proportion of MDS patients with overt dysplasia present with hypocellular BM

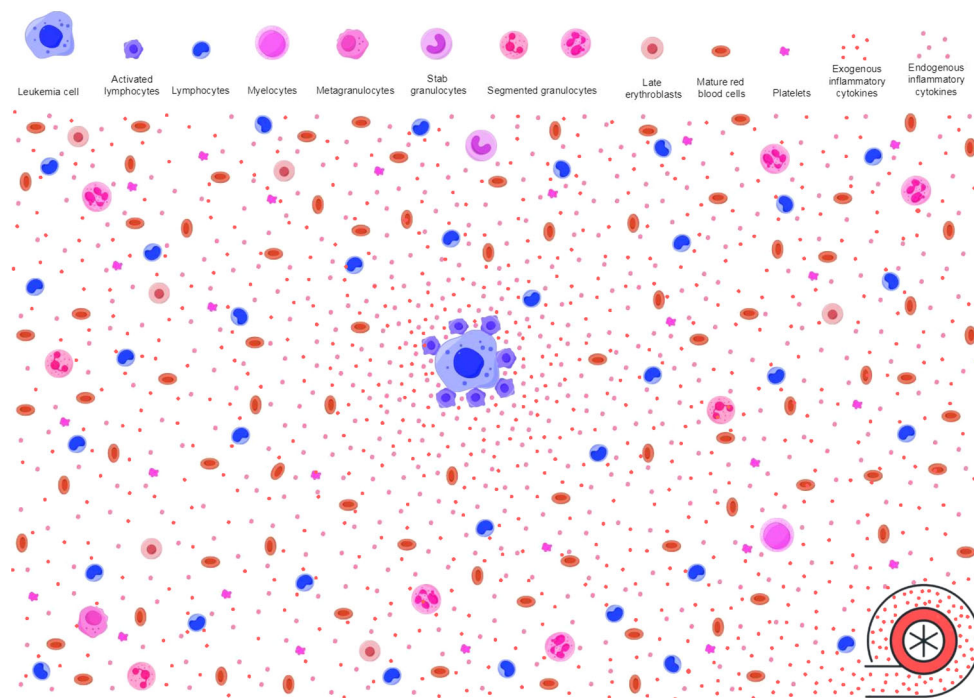


FIGURE 3

Inflammatory stressors power antileukemic activities. As described in Figure 2, immune surveillance in response to neoplastic molecules releases proinflammatory cytokines (endogenous inflammatory cytokines as shown in pink dots) and creates an inflammatory background. However, the baseline antileukemic immunity may not be sufficient to effectively suppress leukemic HPCs. Immune responses to invading microbes produce additional activated immune cells and proinflammatory cytokines (exogenous inflammatory cytokines as shown in red dots). These pathogen-activated immune cells and the proinflammatory cytokines migrate to the inflamed BME through blood circulation, power the primary inflammatory milieu, and enable the antileukemic immunity to achieve an intensity that is sufficient to effectively suppress leukemic HPCs. The primary inflamed BME and extramedullary inflammatory stressors synergistically trigger and sustain AA-like syndrome. HPCs, hematopoietic progenitor cells; BME, bone marrow environment; AA, aplastic anemia.

and peripheral pancytopenia at initial diagnosis or during disease progression and these patients frequently have longer survival (21, 23, 42, 240). Prolonged neutropenia after intensive chemotherapy has been associated with deep remission, longer remission duration, reduced frequency of relapse, and restoration of Th1 immune responses (243, 244). Substantial evidence supports an antileukemic role of autoimmune responses in AHF (42, 95, 102, 232), at least in a large number of AHF patients who have MN-related genetic aberrations (19–26). However, factors underlying the exaggerated autoimmune responses that influence antileukemic activities and disease phenotypes were not discussed in Nissen's manuscript (231).

Inflammatory stressors power antileukemic immunity

The transformation between AHF and clinically overt MNs (MDS with excessive blasts or AML in which an increased percentage of myeloblasts is the most representative parameter in determining leukemic hematopoiesis) can reciprocally occur. The switch that shapes the disease phenotype is a change in the strength of extramedullary inflammatory conditions (33–36). Extramedullary infectious diseases have a conspicuous impact on

phenotypic presentations. During active inflammatory episodes, normal and leukemic hematopoieses are simultaneously suppressed with regression of leukemic blasts on cytological examination and Th1-predominant responses on immunological analysis. Aplastic cytopenia, the disappearance of leukemic blasts, Th1-predominant responses, and a small number of nucleated blood cells for identification of dysplasia result in cytological and immunological features that meet the criteria for the diagnosis of AA (33–36). Following successful control of the inflammatory episodes and a short duration of hematological remission, quickly expanded leukemic clones lead to the appearance of substantial leukemic blasts and symptomatic MNs (33–35). Patients with clinically overt MNs can develop an aplastic crisis during active inflammatory episodes in which systemic inflammatory stress is dramatically aggravated (35, 36). Within this period, the BM becomes aplastic/hypoplastic, and leukemic blasts disappear with the infiltration of autoimmune lymphocytes. These phenomena indicate that autoimmune responses in AHF are an inflammatory stress-powered antileukemic mechanism. Immune surveillance against leukemic blasts contributes to BM-specific autoimmune impairments, while inflammatory stressors strengthen autoimmune responses (as schematized in Figure 3).

This process simulates spontaneous remission in AML patients after an infectious episode and aplastic crisis (245–252). The

mechanism is presumed to be due to reversion of the immune exhaustion state and restoration of antileukemic immunity through activation of immune cells and their secretion of proinflammatory cytokines in response to invading pathogens (250–253). Another frequent situation that induces spontaneous remission is that patients with hypoplastic AML (hAML) are treated with hematopoietic growth factors. To date, spontaneous remission has been reported in more than 200 AML patients. The remission duration usually lasts for 2–6 months, which indicates that leukemic clones cannot be eradicated even under inflammatory stress-powered antileukemic immunity (245, 254). This may be due to the low expression of neoplastic antigens on dormant leukemic cells (255–258). However, repeated spontaneous remissions occur in a paucity of patients (245, 247), which suggests that patients do not completely lose the hematopoietic regulatory mechanisms and the inflammatory stress-powered antileukemic immunity. Another interesting phenomenon also suggests the existence of inflammatory stress-powered antileukemic activities (243, 244). Prolonged neutropenia due to hematopoietic suppression in AML patients after intensive chemotherapy is usually complicated by durable or repeated infectious episodes, which frequently result in death. If patients survive prolonged neutropenia, they may achieve deep remission, longer remission duration, and a reduced frequency of relapse. Recombinant type I inflammatory cytokines (259–262), interferon inducers (263–265), and BCG inoculation (266–268) have been used to treat hematological and non-hematological neoplasms and have shown efficacy in the control of tumor growth or even the clearance of malignant clones. Other vaccine inoculations that can stimulate Th1 responses have also been shown

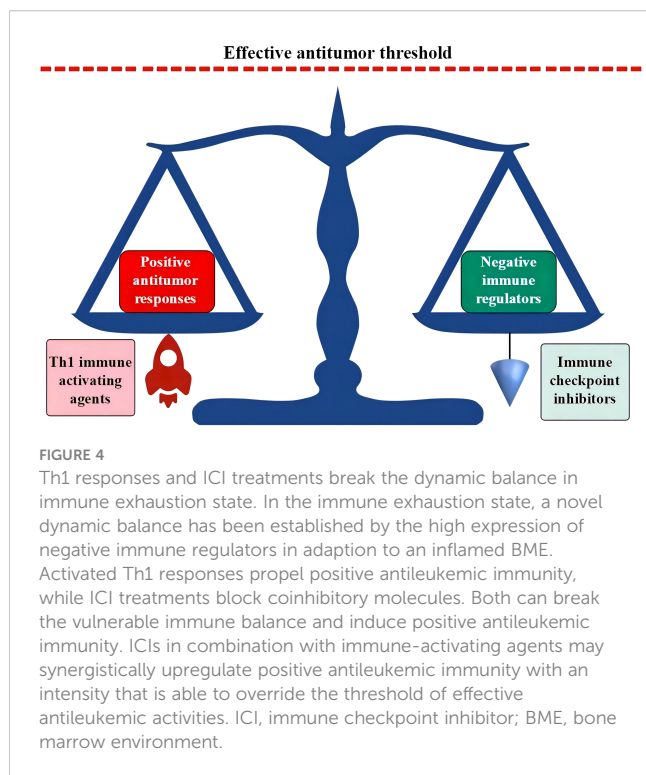
to have antitumor effects (269–271). These non-specific immunological therapies and their treatment effects indicate that inflammatory stressors, rather than antigen-specific responses to invading pathogens, augment antitumor activities (139).

Reversion of the immune-exhausted state by Th1 responses and ICI treatment

Immune exhaustion in adaptation to persistent inflammatory stimulation is a common mechanism underlying the escape of leukemic clones from immune surveillance (17, 18). Hyporesponsiveness is characterized by a high infiltration of negative immune cells, excessive secretion of anti-inflammatory cytokines by immune regulatory cells, and high expression of immune checkpoint molecules on tumor cells in the tumor microenvironment, which work to limit the magnitude of inflammatory responses, avoid excessive tissue damage, and maintain a dynamic immune balance in the context of chronic inflammatory stressors (272, 273). In an immune exhaustion state, dampened antileukemic immunity favors leukemic cell escape from immunological attack and facilitates the penetration of symptomatic MNs. ICIs block coinhibitory molecules and reinvigorate antitumor immunity. ICIs have been successfully used to treat MNs (273–275), and a high-grade inflammatory profile in the BME is a predictor of a good therapeutic response to ICI treatment (276, 277) and suggests that antileukemic immunity is closely related to an inflamed BME. The relationship between an inflamed microenvironment and ICI treatment response has been more thoroughly studied in solid tumors (234, 278–280).

It is widely accepted that dysbiotic gut microbiota plays an important role in promoting tumor cell escape from immune attack in solid tumors (281–283), and the response to ICI treatment is strongly influenced by the abundance and diversity of the gut microbiome (284, 285). This also indicates that antitumor immunity necessitates the engagement of additional antigenic stimulation for immune surveillance against neoplastic antigens. A reduced gut microbial abundance and diversity due to antibiotic treatment can dramatically dampen ICI treatment responses (286). Modulation of the gut microbiota can reverse the dampened responses (287–290). Some pathogenic (291–295) and commensal (296, 297) microbes can stimulate Th1 immune responses and thereby power antitumor immunity (298–300) and enhance ICI treatment responses (301–303). One of the major adverse effects of ICI treatment is hematological toxicity (304–306), especially when treating hematological malignancies and when combined with other antileukemic agents (306). This reinforces the role of Th1 responses in AHF pathogenesis and inflammatory stress-related antileukemic immunity.

Blood cells are immune cells, and their production is regulated largely in response to microbial invasion. Therefore, hematopoietic cells are more sensitive to inflammatory mediators. When



confronting an acute and limited infection, HPCs sense microbial antigens and inflammatory cytokines. With the pathogenic stimulation, host hematopoiesis proliferates and polarizes the differentiation toward the production of effector immune cells to fight invading microbes and replenish the consumed innate immune cells (307–310). However, chronic inflammatory stress in response to persistent intracellular infections can induce Th1-predominant immune responses and exhaust host hematopoietic functions. These responses predominantly exhaust granulopoiesis, erythropoiesis, megakaryocytopoiesis, and B lymphopoiesis (311–316) and result in the morphological and immunological signatures shown in AHF (3, 4, 10, 240). The upregulated expression of HLA-DR, TLRs, and the Nlrp3 inflammasome due to the primary immune-active BME increases sensitivity to antigen stimulation (50, 52, 66, 67) and apoptotic death of HPCs (50, 62, 63). In combination with extramedullary inflammatory stressors, the immune-active BME leads to BM-specific and inflammatory stress-powered autoimmune responses. In the absence of an inflamed BME, some infectious diseases, although able to induce Th1 immune responses, may not seriously injure hematopoietic function. Evidence for this is that patients with systemic rheumatic diseases are seldom complicated by AHF. Along with the persistence and exacerbation of inflammatory stressors, the host immune system can be impaired, which changes the immunological landscape from the proinflammatory phenotype of AHF to the immune exhaustion phenotype of advanced MN (317–320). Exhausted immune responses and DNA damage occurring under chronic inflammatory conditions are considered major contributors to the immune escape of leukemic cells (15, 16, 321, 322). The role of immune exhaustion in advanced MN may cause an increased threshold for effective antileukemic immunity (323). Enforcing an additional antigen stimulation or administering ICIs can reverse the immune exhaustion state and thereby overcome the raised threshold and restore missed antileukemic immunity (35, 95, 250, 253, 323). Combination of immune-stimulating agents and ICI treatments may further potentiate antitumor activities (as schematized in Figure 4).

From this point of view, AHF and MNs have complex intrinsic relationships, and some patients with definitively diagnosed AA may be hMDS (39, 40, 324, 325) or hAML (102, 232). The absence of overt leukemic hematopoiesis in AHF likely results from the small number of nucleated cells available for identification of aplasia and leukemic blasts due to severe BM hypoplasia and a preferential attack on transformed HPCs by autoimmune CTLs and their secretion of hematopoietic inhibitory mediators (238, 239, 259–262). Indeed, neutropenia is a common preleukemic presentation in MNs, and in a significant proportion of MDS patients, neutropenia can be a solitary hematological abnormality that persists for many years (241, 242). Furthermore, a poor response to hematopoietic growth factors predicts a high frequency of disease progression (242). A decreased white blood cell count and concealed leukemic clones make it difficult to distinguish this AA-like syndrome from genuine AA (39, 40, 324, 325), which leads to a diagnosis of AA in most circumstances (3, 4), especially before the wide application of NGS in the diagnosis and stratification of hematological diseases.

Decreased inflammatory strength facilitates leukemic transformation

AHF is an organ-specific AID. Autoimmune responses occur predominantly in the BM and result in the exhaustion of HPCs and impairment of mature blood cell production (1, 2, 39, 240). AA and hMDS are clonal hematological diseases (5, 25, 27, 240). Genetic aberrations in clonal hematopoiesis affect cell proliferation, self-renewal, and apoptosis (5–8). While hMDS is an unequivocal MN, AA has a high frequency of transformation to MNs. The natural evolution from AA to MNs is usually a long-term process (11–14) and is frequently attributed to genetic damage or immune exhaustion due to an inflamed BME (15–18). However, leukemic transformation can occur during or shortly after IST (19–23). Effective treatment of underlying infections can also induce leukemic transformation (33–35). Prior to the emergence of symptomatic MNs, patients usually experience a short duration of hematological remission. Leukemic transformation shortly after IST or treatment of underlying infections may better reflect the intrinsic relationship between AHF and MNs with regard to the influence of the host immunological state on the disease phenotype. This is because IST and treatment of underlying infections can rapidly change the host immune state without inducing novel genetic damage. An aplastic crisis with leukemic cell regression in definitively diagnosed MNs during inflammatory episodes provides a more persuasive argument for the influence of the host immune state on the disease phenotype (35, 36).

How should we interpret BM-predominant autoimmune impairment in AHF when considering the very high prevalence of chronic inflammatory disorders in the gastrointestinal tract and other organ systems?

A reasonable explanation is that, similar to the microenvironment in solid tumors (233, 234, 272, 279), primary autoimmune pathogenesis targets specific antigens or DAMPs on HPCs or other blood cells in the BM, regardless of whether the targeted antigens are infectious (84–87) or neoplastic (95–102). Interactions between autoimmune CTLs and targeted antigens (50, 59, 100, 232) or between innate immune cells and DAMPs (95–98) evoke an inflammatory background in the BME (27, 93, 94, 236), which determines the BM-predominant autoimmunity. Defects in HPCs (77) and derangement of immune responses (78) are present not only in active SAA but also in hematological remission following IST, which suggests that intrinsic abnormalities in HPCs are responsible for the primary autoimmune response. Like patients with AA (326–331), patients with MDS and AML have also been shown to have a high frequency of autoantibodies that can bind erythrocytes, erythroblasts, and platelets (42, 99–102, 258), and autoantibodies against hematopoietic progenitors can directly induce Th1 immune responses (100, 102, 332, 333). Patients with these autoantibodies frequently present with hypoplasia and

absence of dysplasia, which resembles a clinical phenotype observed in patients with AA (21, 42, 102).

How should we interpret leukemic cell regression in the SAA stage and their dysregulated proliferation after the successful control of underlying inflammatory stressors?

A reasonable explanation is that targeted molecules are present in leukemic blasts (50, 59, 88, 100, 102). Neoplastic epitopes from genetic or epigenetic products of transformed HPCs (42, 93, 95, 97, 100, 232) are likely the targeting molecules responsible for the primary inflammatory BME. However, effective repression of leukemic blasts also requires the engagement of additional inflammatory stressors that are strong Th1 responses for the sustenance of antileukemic immunity (95, 161, 245, 246, 250). This is perhaps due to the low immunogenicity of neoplastic antigens on leukemic cells (255–258). Additional inflammatory stressors may play a role in sustaining a systemic inflammatory state (201–203), which together with the primary inflammatory BME creates an inflammatory niche with an intensity sufficient to repress normal and leukemic hematopoieses and synergistically forms the characteristic immunological signature in AHF. Th1 responses repress granulopoiesis, erythropoiesis, megakaryocytopoiesis, and B lymphopoiesis (311–317) in accordance with the cytological signature in AHF (3, 4, 10, 240). Th1 responses from extramedullary infectious diseases may preferentially strengthen antileukemic immunity in these lineages. ICIs for the treatment of hematological and non-hematological malignancies may also benefit from inflammatory stress-powered antitumor immunity. The administration of ICIs reverses the immune exhaustion state, promotes the infiltration of proinflammatory immune cells into the tumor microenvironment, and reduces the threshold for inducing effective antileukemic immunity (272–275). Inflammatory strength in the tumor microenvironment predicts the treatment response to ICIs (276–280). However, effective antitumor immunity requires additional antigen stimulation especially from the gastrointestinal tract (281–285), and the dynamic microbial ecosystem is the most important environmental factor for maintaining host immune homeostasis (146–148). Some pathogenic (291–295) and commensal (296, 297) microbes can stimulate Th1 responses, enhance ICI treatment-induced antitumor immunity (301–303), and even directly overcome the immune exhaustion state (298–300). This mechanism may play a more important role in MNs because blood cells are immune cells and their production is regulated largely in response to pathogen invasion (307–310). During active inflammatory episodes, TH1 immunity in response to invading pathogens powers antileukemic effects, which results in the regression of leukemic clones (33–36). After successful control of inflammatory diseases, suppressive effects on leukemic clones are mitigated and result in the penetration of morphologically identifiable leukemic hematopoiesis (35).

How should we interpret the very short interval spanning the leukemic transformation process when considering that the development of symptomatic MNs through the acquisition and accumulation of novel oncogenic mutations is unlikely within such a short interval?

A reasonable explanation is that leukemic clones preexist but are repressed in AHF stages (19–27) and rapidly expand after the resolution of inflammatory stressors (95, 245, 250, 254). The persistence of autoantibodies (42, 99, 100, 258, 330) and autoimmune responses (59, 78, 93, 273, 321) in AA, MDS, and AML suggests that autoantigens are persistent and their immunogenicity is less intensive. Leukemic clones cannot be eradicated even in inflammatory stress-powered antileukemic immunity, which is perhaps due to the low expression of neoplastic antigens and immune molecules in dormant leukemic cells (35, 245, 250, 254). During an inflammatory episode against invading pathogens that can stimulate strong Th1 responses, a patient's immune system is mobilized, and the vulnerable immune balance in adaptation to chronic inflammation is disrupted, which results in the recall of antileukemic immunity and concealment of leukemic blasts. This process is similar to that observed in spontaneous remission in AML patients after an infectious episode (35, 245, 250). During infectious episodes, patients demonstrate positive immune responses and frequently experience an aplastic crisis. After successful treatment of underlying infections, dampened inflammatory stress-powered antileukemic immunity leads to the expansion of previously suppressed leukemic clones and facilitates the appearance of symptomatic MNs, which is distinct from the naturally occurring clonal evolution in AA (11–14) due to the acquisition of novel somatic mutations and immune exhaustion in the chronic inflammatory milieu (16, 17, 321, 323).

How should we interpret the short duration of hematological remission before the emergence of symptomatic MNs?

Prior to the emergence of symptomatic MNs, whether following IST (19–23) or effective treatment of underlying infectious diseases (33–35), patients experience a short duration of hematopoietic remission. A reasonable explanation for this short remission duration is that inflammatory stress-powered antileukemic activities can simultaneously repress normal (54–57) and malignant (245–254) hematopoiesis, which results in BM hypoplasia/aplasia with the infiltration of autoimmune lymphocytes and an increase in inflammatory intensity (34, 35). The absence of leukemic blasts may be due to the preferential repression of malignant proliferation (238, 239, 259, 260) and the small number of nucleated blood cells available for the identification of dysplastic features (232, 240, 324, 325). Following

the effective treatment of underlying infections, inflammatory stress-mediated antileukemic activities are mitigated, which leads to the simultaneous proliferation of normal and leukemic hematopoieses and transient clinical remission (33–35) due to the prolonged proliferative cycle of damaged HPCs (334–336). Along with an increase in leukemic cell burden due to dysregulated proliferative capacity (5–8), leukemic cells compromise the hematopoietic pool and outcompete their normal counterparts. Normal hematopoiesis is subsequently suppressed (337–340), which leads to the emergence of symptomatic MNs. The panorama of inflammatory stress-powered antileukemic immunity is better displayed in our reported patient with definitively diagnosed MDS with excessive blasts-1 who developed an aplastic crisis during an inflammatory episode (35). During the aplastic crisis, leukemic blasts regressed with atypical lymphocyte infiltration in the BM. Tentative antituberculosis treatment resulted in not only the disappearance of the atypical lymphocytes but also an increase in leukemic blasts.

How should we interpret leukemic transformation during or shortly after ATG-based IST?

Approximately 70%–80% of SAA patients respond to ATG-based IST (19–23). However, dysregulation of the immune system and defects in HPCs persist even in remission patients (77, 78), and relapse eventually occurs in 30%–40% of responding patients (19–23), which indicates that the primary pathogenic factor is not removed by IST. In approximately 10%–15% of SAA patients, the disease phenotype transforms to MNs. In some cases, leukemic transformation occurs during or shortly after IST (19–23). Some MN-related somatic mutations in the SAA stage predict a lower frequency of deep hematologic response and a higher rate of disease relapse and leukemic transformation. Non-responding patients carry a higher frequency of these unfavorable mutations compared to responding patients (21–24). The presence of MN-related genetic aberrations influences treatment responses, which indicates that genetic damage in HPCs plays an important role in eliciting autoimmune pathogenesis. The pharmacologic role of ATG-based IST in AHF treatment is to deplete effector CTLs and induce immune tolerance; thus, IST functions as an immune suppressant to relieve autoimmune impairment in HPCs (28–32). At the same time, inflammatory stress-mediated antileukemic immunity can be compromised. After IST, the number and size of somatic mutations are massively increased (20, 42) due to the mitigation of inflammatory stress-powered antileukemic immunity. From this point of view, IST promotes the penetration of symptomatic MNs by interfering with the process of immunological attack, which is distinct from the removal of antigen stimulation by treating underlying infections. However, their effects are similar. Both IST and treatment of underlying infections can mitigate the intensity of the inflamed BME and promote the penetration of symptomatic MNs. Intriguingly, approximately one-third of patients who respond to IST do not relapse or progress to MNs, which supports the heterogeneous nature of the etiology and pathology that initiates

and sustains autoimmune-mediated hematopoietic injuries. More interestingly, transient genetic aberrations occasionally occur in a paucity of patients after IST (19, 20). It is possible that some genetic aberrations are not correlated with or not sufficient for leukemic transformation (24, 25, 27).

Particular attention should be given to gut inflammatory disorders and disseminated tuberculosis in AHF patients

Although patients with MNs may benefit from inflammatory stress-powered antileukemic immunity, an excessive inflammatory cascade and severe cytopenia can be harmful or even fatal. Like in other AIDs (156–161), AHF pathogenesis necessitates an active chronic inflammatory condition in addition to the inflamed BME to sustain BM-predominant autoimmune impairment (90, 95, 161, 313, 315). When AHF patients present with active inflammatory symptoms and their cytopenia is dramatically exacerbated, identifying and disposing of inflammatory niduses are urgent tasks that are needed to save patients' lives. In this situation, particular attention should be given to inflammatory diseases in the gastrointestinal tract and disseminated tuberculosis. Tuberculosis reactivation may be the result of an immune exhausted state and/or the administration of immune suppressants. Disseminated tuberculosis can worsen hematopoietic function and become a major health problem in AHF patients.

Association of gut inflammation with AHF pathogenesis

An association between AHF and gut inflammatory conditions has long been proposed (89, 90, 341). Patients with AA have a dysbiotic gut microbiota (342), and the immunological signature of AA is the same as that of IBD (343), which suggests that AA and IBD may share similar initiating factors and common pathogenic agents (1, 2, 344, 345). A gluten-free diet for coeliac disease-associated aplastic cytopenia (346) or resection of diseased colonic segments in patients with neutropenic enterocolitis (347) can effectively relieve hematopoietic suppression. In our previous report (348), two cycles of intermittent hematopoietic recovery and disease relapse occurred in a patient with refractory SAA following intermittent treatment with a gut-cleansing preparation, which reinforces the definitive role of gut inflammatory conditions in AHF pathogenesis. The contribution of the gut microbiome to sustaining the pathogenesis of graft-versus-host disease after allogeneic hematopoietic stem cell transplantation, a pathogenic mechanism similar to that of AA and frequently used to study AHF pathogenesis in animal models, was reported several decades ago (161). In our retrospective study, all patients with SAA had imaging abnormalities that reflected the existence of chronic inflammatory lesions and acutely aggravated inflammatory damage in the gastrointestinal tract during inflammatory episodes and exacerbated cytopenia (349). Similar to

non-hematological AIDs (156–160), growing evidence demonstrates that the gastrointestinal tract is the most common inflammatory nidus that sustains AHF pathogenesis in patients with a background of an inflamed BME (89, 90). Aggravated gut inflammatory disorders can strengthen the immune-active BME and suppress normal and leukemic hematopoieses, which leads to AHF and regression of leukemic clones (33–36). The effective treatment of gut inflammatory conditions can ameliorate AHF (348) and promote leukemic transformation (33).

Hematopoietic suppression by Th1 responses to tuberculosis

The Th1 immune response is the major mechanism involved in defense against *Mycobacterium tuberculosis*, with IFN- γ production playing a pivotal role in combating *M. tuberculosis* infection (291, 350, 351). IFN- γ is the most important mediator of AHF development (55, 56, 240) and links AHF pathogenesis with chronic infectious diseases that provoke Th1-predominant immune responses. Tuberculosis is one of the most common chronic intracellular infections (106, 209, 315). Over 90% of the world's population has been infected by *M. tuberculosis*. Despite great therapeutic advances, nearly a quarter of individuals remain latently infected after the initial infection (352–354). Latent tuberculosis can be reactivated under certain circumstances such as with aging, undernourishment, prolonged psychological stress, long-term administration of immune suppressants, or coinfections with HIV or other pathogenic microbes (355–357). In this situation, antituberculosis immunity by trained Th1 cells (291, 358), CTLs (359, 360), NK/NKT cells (361, 362), unconventional lymphocytes (363, 364), and even CD5+ B cells (365) can be recalled. These memory immune cells rapidly expand and produce a substantial amount of IFN- γ , TNF- α , and other proinflammatory cytokines in response to increased *M. tuberculosis* antigen load. Excessive proinflammatory cytokines strengthen the primary immune-active BME and repress normal and leukemic hematopoieses (34, 35, 106, 315). Antigens of *M. tuberculosis* may also cross-react with autoantigens on HPCs. With the cross-reaction, reactivated effector immune cells induce an immunological attack on HPCs and strengthen the inflamed BME (88). Even in latent tuberculosis, chronic antigen stimulation may persist due to the high heterogeneity of this chronic infection (356, 365–367) and fluctuations in host performance status, which leads to fluctuating chronic inflammation.

The more important role of gut involvement in tuberculosis infection

Disseminated tuberculosis (368–371) or even disseminated BCG vaccination (372) can induce BM hypoplasia and peripheral cytopenia. The fact that tuberculosis-induced AHF occurs only in disseminated tuberculosis instead of in isolated pulmonary tuberculosis suggests that tuberculosis can infect hematopoietic tissues (373) or the gastrointestinal tract (34, 35, 181, 349). Gut involvement and subsequent dysbiosis (181) likely play more important roles in inducing systemic inflammatory disorders

(374, 375). In our retrospective study investigating infectious niduses during flared inflammatory episodes and accelerated cytopenia, five of 17 recruited SAA patients had imaging abnormalities suggestive of tuberculosis reactivation, all of which involved inflammatory diseases in the gastrointestinal tract (349). The incidence of tuberculosis reactivation may be even greater in advanced MN patients (376–378). It is not surprising that there is a high incidence of chronic *M. tuberculosis* infection in AHF patients because patients with HLA-DR15 have weaker responses to *M. tuberculosis* (379, 380), and AHF patients have a high frequency of HLA-DR15 phenotype (52, 53). Gastrointestinal and even isolated pulmonary tuberculosis can induce pathological processes in the gastrointestinal tract, not only alone but also in combination with gut dysbiosis, which results in diffuse gut inflammatory lesions (181, 381, 382). In this setting, both pathogenic and commensal (185, 186) microbes, in addition to *M. tuberculosis* infection (315, 316), become exogenous antigens to sustain deranged immune responses.

Summary and perspective

Autoimmune responses in AHF may represent an inflammatory stress-powered antileukemic mechanism, at least in a significant proportion of patients whose pathogenesis is associated with MN-related genetic aberrations. With age, the incidence of clonal hematopoiesis increases, which is known as mutation-specific adaptation to environmental stressors and is consistent with a high incidence of AHF and inflammatory disorders in old age. However, age-related clonal hematopoiesis also increases the risk of malignant evolution (383–385). A dynamic balance between antileukemic activities and negative immune regulators may play a more important role in the suppression of transformed HPCs and the maintenance of effective hematopoiesis in old age. In this process, immune surveillance against neoplastic antigens or DAMPs initiates a primary inflammatory background in the BME and may contribute to the BM-specific autoimmune impairment. Extramedullary inflammatory stressors generated from exogenous antigen stimulation, especially from the gastrointestinal tract and chronic intracellular infections, play a critical role in the sustenance of autoimmune responses and the apoptosis of HPCs and promote the development of AA-like syndrome.

Although AA and MNs are generally considered distinctive disease entities, the phenotype of aplastic cytopenia can transform into MNs and vice versa. The switch that shapes the disease phenotype is a change in inflammation strength. During active infectious episodes, leukemic blasts can regress due to the reversion of the immune exhaustion state and the restoration of antileukemic activities. At this time, patients manifest aplastic cytopenia. After successful treatment of underlying infections, leukemic clones rapidly expand, and patients manifest symptomatic MNs, which commonly follow a short duration of hematological remission. Miscellaneous microbes or even endotoxins can induce antitumor immunity. This indicates that not antigen-specific stimulation but rather inflammatory stressors in response to microbial invasion are responsible for sustaining antitumor activities. Although they occur through different mechanisms, the effect of ATG-based IST is

similar to that of treating underlying infections. Spontaneous remission in AML patients and non-specific immunological therapies in treating hematological malignancies may share an inflammatory stress-powered antileukemic mechanism.

An in-depth investigation of inflammatory stress-powered antileukemic immunity is highly important for theoretical research and clinical practice. Understanding the mechanisms of immune surveillance against malignant proliferation and the rational administration of immune-activating agents and ICIs in the treatment of hematological malignancies will be helpful, especially when aplastic cytopenia appears to be the major adverse effect. Some pathogenic microbes can stimulate Th1 responses. Inoculation of vaccines from these microbes has direct antileukemic effects and enhances ICI treatment efficacy. The inflammatory stress-powered antileukemic mechanism raises many questions.

- 1) Despite powering antileukemic immunity, chronic antigen stimulation may further exhaust the host immune system and upregulate the responsive threshold. These effects may lead to a requirement for more intensive antigen stimulation to achieve effective antileukemic strength, which forms a vicious cycle and attenuates antileukemic activities. This raises the question of how to take advantage of non-specific inoculation for the treatment of MNs without inducing immune exhaustion; intermittent inoculation in combination with ICI treatment is likely a superior option (348, 386, 387).
- 2) ICI treatments lower the response threshold, while inoculations enforce the response strength. ICI treatments in combination with inoculation may synergistically reinvigorate missed antileukemic activities and further enhance treatment efficacy. This combination therapy may produce an overwhelming inflammatory cascade and heavy hematopoietic suppression. This fatal side effect raises the question of how to tip the balance between benefits and severe toxicity and how to combine immunological therapies.
- 3) While some commensal microbes can stimulate Th1 responses and exhibit antileukemic activities, some microbes can suppress Th1 responses and favor the maintenance of an immune exhaustion state. However, the abundance and diversity of the gut microbiota are critical for the integrity and function of the gastrointestinal tract. Gut dysbiosis and excessive Th1 responses disrupt the intestinal integrity and barrier function and induce gut inflammatory conditions (147, 183, 197, 345). Furthermore, chronic gut inflammatory conditions can induce systemic immune dysregulation and immune exhaustion. This raises the question of how to exploit immune responses to “beneficial microbes” and avoid severe gut inflammatory damage.
- 4) Both AHF and MNs are fatal diseases. The resolution of inflammatory stressors by either IST or treatment of underlying diseases may lead to phenotypic

transformation from AHF to clinically overt MNs, which complicates the patients’ disease course. This raises the question of how to assess the benefits and risks of leukemic transformation prior to IST. Additionally, underlying inflammatory conditions should also be properly managed.

- 5) Different lineages of immune cells are regulated by different cytokines in response to different antigen stimulation (307–310). Blood cells are immune cells, and MNs can be derived from different cell lineages (10). Some cytokines inhibit certain lineages of leukemic clones but may promote the proliferation of others (388). This raises the question of what leukemic cells of origin can benefit from and which ones may be promoted by the treatment with immune-activating agents.
- 6) It is unclear what antigens are neoplastic, what neoplastic antigens are immunogenic, and what intensity of immunogenic antigens can provoke antileukemic immunity. Although antileukemic immunity is powered by non-specific antigenic stimulation and immunogenic antigens responsible for antileukemic immunity may be miscellaneous in different neoplasms, is there any advantage in selecting an inoculation microbe with epitopes that cross-react with neoplastic antigens if the neoplastic antigens are identified?

Collectively, inflammatory stress-powered antileukemic immunity warrants extensive investigation. This may explore a new way of MN treatment. With in-depth investigations, many questions will emerge, and better strategies for improving treatment responses and managing adverse complications will be found.

Author contributions

X-CZ: Conceptualization, Writing – original draft. BJ: Data curation, Writing – original draft. N-NX: Data curation, Writing – original draft. X-YS: Data curation, Writing – original draft. F-JM: Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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