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Review

Hematological malignancies and autoimmune hemolytic anemia in systemic lupus erythematosus patients: A literature review

Kacper Siemek[1], Katarzyna Wojakowicz[1], Zuzanna Rzepkowska[1], Oliwia Kubiś[1], Jakub Mastalerz[2], Magdalena Szmyrka[3]

[1]Students' Scientific Club of Rheumatology, Wroclaw Medical University, Poland
[2]Dolnośląskie Centrum Onkologii, Pulmonologii i Hematologii, Wrocław / Lower Silesian Center for Oncology, Pulmonology and Hematology, Wroclaw, Poland
[3]Independent researcher

Address for correspondence:
Jakub Mastalerz
Dolnośląskie Centrum Onkologii, Pulmonologii i Hematologii
pl. Ludwika Hirszfelda 12, 53-413 Wrocław
tel. +48 795 106 055
e-mail: jakub.mastalerz18@gmail.com

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by immune dysregulation and a wide spectrum of clinical manifestations, including significant hematological involvement. The objective of this review was to summarize the epidemiology, pathogenic mechanisms, and treatment approaches for hematological malignancies (HMs) and autoimmune hemolytic anemia (AIHA) in patients with SLE, integrating recent advances in diagnosis and therapy. We conducted a narrative review of meta-analyses, large population-based studies, and translational research addressing lymphoma, leukemia, multiple myeloma, and AIHA in the context of SLE. Findings consistently demonstrate an increased standardized incidence ratio (SIR) for HMs, particularly non-Hodgkin's lymphoma (SIR ≈ 5.7), with elevated risks also reported for Hodgkin lymphoma, leukemias (acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia), and multiple myeloma (SIR ≈ 1.5). Pathogenesis is multifactorial, involving chronic immune activation, Epstein-Barr virus reactivation, oxidative stress, impaired DNA repair, and cumulative exposure to alkylating agents. AIHA, most commonly warm-antibody mediated, represents an additional source of morbidity, often complicating treatment decisions. Corticosteroids remain the first-line therapy, while refractory disease benefits from rituximab or cytotoxic immunosuppressants. Novel therapeutic strategies, including complement inhibitors (sutimlimab, pegcetacoplan), Bruton tyrosine kinase inhibitors, and neonatal Fc receptor antagonists, are emerging as promising options to reduce relapse rates and steroid dependence. Early recognition, individualized immunosuppressive regimens, and incorporation of targeted therapies may improve survival and long-term outcomes in this high-risk population.

KEYWORDS

systemic lupus erythematosus, hematologic neoplasms, autoimmune hemolytic anemia, non-Hodgkin's lymphoma

1. Introduction

Systemic lupus erythematosus (SLE) is a prototypical systemic autoimmune disease with heterogeneous clinical manifestations and a complex pathogenesis involving genetic, environmental, hormonal, and immunological factors. Advances in diagnostic criteria, monitoring strategies, and therapeutic interventions have substantially improved survival rates of SLE patients over recent decades. However, with longer life expectancy, new long-term complications have emerged, including an increased incidence of malignancies.

Hematological abnormalities are frequent in SLE and may range from benign cytopenias to life-threatening conditions. Two major aspects have drawn particular attention in recent years: the

increased risk of hematological malignancies (HMs) and the occurrence of autoimmune hemolytic anemia (AIHA).

Epidemiological studies consistently show that individuals with SLE are at higher risk of developing cancer compared to the general population, with HMs – particularly lymphomas – being the most frequently reported [1,2,3]. The mechanisms underlying this increased risk are likely multifactorial, encompassing chronic immune stimulation, persistent inflammation, defects in apoptosis, impaired immune surveillance, and the potential oncogenic effects of immunosuppressive therapies [1,4,5]. Importantly, this association highlights the delicate balance between controlling autoimmune activity and avoiding long-term adverse effects of treatment [1,5].

In parallel, autoimmune cytopenias, and especially AIHA, represent clinically significant complications of SLE. AIHA may present at disease onset or during its course, often contributing to morbidity and complicating therapeutic decision-making [6]. Although the pathophysiology of AIHA in SLE remains incompletely elucidated, autoantibody-mediated destruction of red blood cells is central, with disease activity, treatment exposures, and genetic predispositions acting as modulators [7,8]. Importantly, AIHA in the context of SLE not only influences prognosis but may also overlap with the risk of malignant transformation, further complicating patient management [9].

Taken together, HMs and AIHA represent two distinct yet interconnected dimensions of hematological involvement in SLE.

Despite the growing body of evidence, many aspects of the relationship between SLE and HMs remain unclear. Current literature points to distinct patterns of risk, differences in clinical presentation, and variable outcomes in comparison with malignancies arising in the general population. A better understanding of these associations is essential for developing effective surveillance strategies, guiding therapeutic decisions, and improving overall patient care.

2. Material and methods

This article is a narrative review synthesizing available evidence on HMs and AIHA in SLE. A comprehensive literature search was performed in PubMed/MEDLINE, covering publications up to September 2025. Search terms included combinations of: “systemic lupus erythematosus,” “autoimmune hemolytic anemia,” “hematologic malignancy,” “lymphoma,” “leukemia,” “B-cell dysregulation,” “complement pathway,” and “targeted therapy,” linked by Boolean operators. Inclusion criteria encompassed: publications in English; meta-analyses, systematic reviews, original cohort and case-control studies, and population-based registries; case reports and case series providing unique clinical insights; and studies involving SLE patients diagnosed per established classification criteria (ACR/EULAR), addressing malignancy risk, AIHA prevalence, shared molecular pathways, or pharmacological interventions.

Exclusion criteria comprised: non-English publications; studies focusing solely on non-hematologic malignancies; conference abstracts lacking sufficient methodological detail; and studies without clearly defined diagnostic criteria.

In total, 87 publications were included . Data extraction focused on: incidence and standardized incidence ratios (SIRs) of HMs in SLE; prevalent malignancy subtypes, particularly diffuse large B-cell lymphoma (DLBCL); molecular and genetic mechanisms linking SLE to HMs; clinical risk factors including sex, age at diagnosis, therapy exposure, and disease activity; prevalence, pathophysiology, and risk factors of AIHA in SLE; and an overview of novel AIHA treatment strategies. The overview of individual patients was presented in a structured table encompassing patient characteristics, clinical manifestations, diagnostic findings, treatment modalities, and outcomes.

3. Hematological malignancies in SLE patients

An umbrella review, published in 2025, based on 34 meta-analyses showed that patients with SLE had higher than average risk of developing HMs [10].

Among HMs reported in patients with SLE, the most frequently described are non-Hodgkin's lymphomas (NHLs), particularly DLBCL, as well as Hodgkin lymphoma, various forms of leukemia – both acute (acute myeloid leukemia – AML, acute lymphoblastic leukemia – ALL) and chronic (chronic lymphocytic leukemia – CLL, chronic myeloid leukemia – CML) – and multiple myeloma [10,11].

A cohort meta-analysis involving nearly 68,000 patients with SLE demonstrated significantly elevated SIRs for all HMs (SIR = 2.9), with the highest increase observed for NHL (SIR = 5.7), followed by Hodgkin lymphoma (SIR = 3.1), leukemia (SIR = 2.3), and multiple myeloma (SIR = 1.5) [3]. Data from international registries confirm this trend, indicating an approximately threefold higher risk of hematological neoplasms in SLE patients [12].

Moreover, another meta-analysis, evaluating 40 malignancies, identified an increased risk of cancer in SLE patients by 18%, with a significantly higher risk for NHL, Hodgkin lymphoma, leukemia, and multiple myeloma [13]. Furthermore, another study reported that the SIR for cancer in patients with autoimmune diseases (AID) was 3.37, while for SLE alone, it was 2.58, indicating that among AID, SLE had a relatively lower, but still significant, cancer risk [14].

A single-center retrospective analysis from Poland revealed that among 932 patients with SLE treated in Kraków, 9.87% had a cancer diagnosis, with HM accounting for 16.3% of these cases [11]. Patients with malignancy tended to have an older age at SLE onset, longer disease duration, and typical clinical features such as weight loss and fatigue. They were also more likely to present with organ complications and to have received aggressive treatment, including cyclophosphamide.

Additionally, a larger epidemiological assessment [13] identified markedly increased risks of NHL and Hodgkin lymphoma (more than threefold), myeloma and liver cancer (over twofold), as well as

a moderate rise in risk for cervical, lung, bladder, and thyroid cancers (≥ 1.5-fold). Conversely, the risks of breast, endometrial, melanoma, and prostate cancers were significantly reduced [13].

Clinical cohort studies have also demonstrated an increased incidence of solid tumors, including breast, cervical, colorectal, lung, and gastric cancers [10,11]. Conclusions highlight not only the increased risk of HM but also oral and pharyngeal neoplasms, alongside a reduced risk of uterine, endometrial, and melanoma cancers [10,11].

3.1. Diffuse large B-cell lymphoma

Most studies consistently report NHL as the most prevalent HM in SLE patients, with DLBCL being the most common subtype [15,16,17].

This is why genes shared between SLE and DLBCL were analyzed in various studies. The Immune Imbalance Transcriptomics algorithm also revealed enrichment in immune-related pathways [18]. Li et al. [19] identified 54 differentially expressed genes shared between SLE and DLBCL. Decreased expression levels of genes *GPR84* and *IFIT3* were linked to enhanced immune therapy sensitivity and better overall survival and progression-free survival in DLBCL patients. A year later a study conducted by Hejrati et al. [20] found altered expression of 146 genes leading to dysregulation of the immune system and its mediators. 5 hub genes (*IFIT3*, *IFIT1*, *DDX58*, *CCL2*, and *OASL*) emerged as key factors were predicted to hold crucial roles in the underlying molecular mechanisms.

Additionally, chronic immune stimulation, persistent viral infections (such as Epstein-Barr virus and hepatitis viruses), oxidative stress, autoantibody profiles and dysfunction of the tumor necrosis factor and other pathways were also proposed as potential mechanisms contributing to malignancy development (Figure 1) [1,21,22].

Furthermore, older age at SLE diagnosis was identified as an independent risk factor for developing HM. Conversely, female sex and hydroxychloroquine use were found to be protective factors against mortality in SLE patients [23].

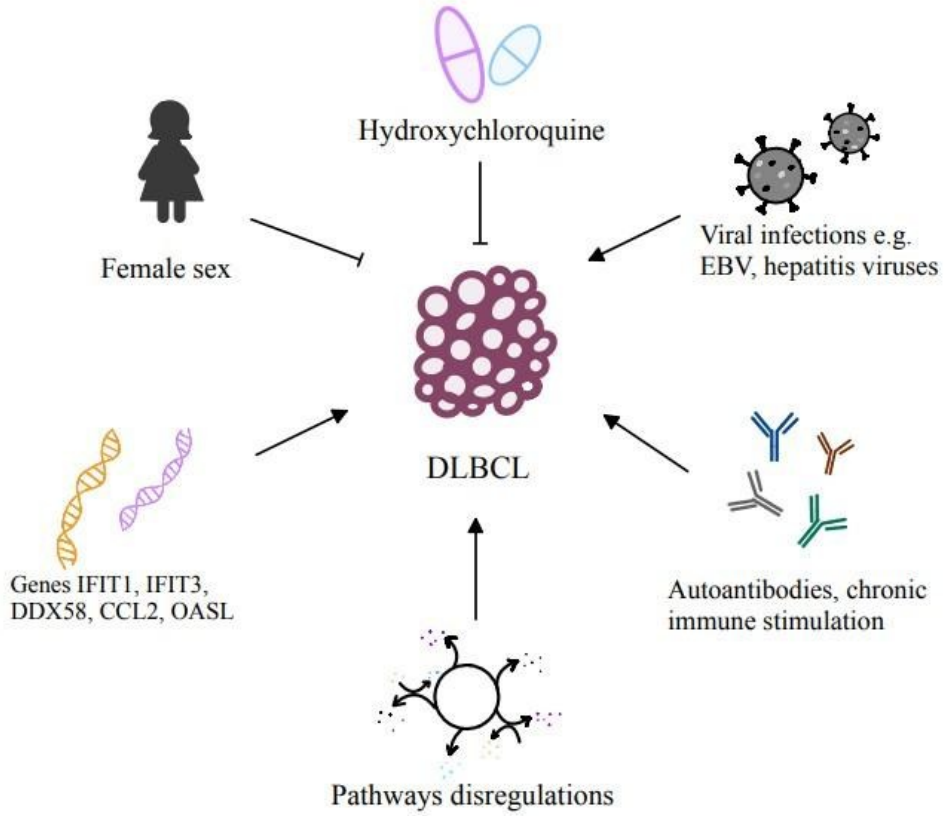

Fig. 1. DLBCL-development influencing factors

3.2. Lymphoma

Lymphomas should be considered in the differential diagnosis of neoplastic lesions emerging in SLE patients, which can be proven by numerous case studies [24,25,26,27,28,29,30].

There is debate regarding the typical timeframe in which lymphoma develops following an AID diagnosis. Zhang et al. [22] confirmed the previous findings, that the risk ratio of HM is highest within the first year after SLE diagnosis and declines over time [31,32]. Martín-López et al. [23] however, found the median duration of SLE to be 9 years before the development of lymphoma. On the other hand, a recent mendelian randomization study contradicts those reported in previous traditional observational studies, stating that no significant associations were found between SLE and NHL risk [33]. This highlights the need for future studies with different datasets, approaches, and populations to further examine the potential associations between these AID and the risk of NHL.

The prognosis for male patients with SLE is generally poorer, especially when complicated by HM. Therefore, further research is needed to explore the relationship between the antinuclear antibody spectrum, medication use, and the development of HM in SLE [22].

3.3. Acute myeloid leukemia and acute lymphoblastic leukemia

Cohort meta-analyses including tens of thousands of patients demonstrated a significantly increased risk of leukemias compared with the general population, with elevated SIRs reported for both AML and ALL [1]. The development of AML and ALL in SLE patients has been linked to iatrogenic DNA damage induced by cytotoxic drugs, chronic inflammation, and defects in DNA repair mechanisms [1]. Alkylating agents, particularly cyclophosphamide and melphalan, as well as topoisomerase II inhibitors, induce characteristic chromosomal mutations, such as deletions of chromosomes 5 and 7 or 11q23 translocations, predisposing to therapy-related AML/MDS [34,35]. Cyclophosphamide has been strongly associated with t-AML/t-MDS in a dose-dependent manner, with a clear dose–response relationship observed [36,37]. Furthermore, chronic immune activation in SLE, excessive production of reactive oxygen species, and polymorphisms in DNA repair genes may contribute to mutation accumulation in hematopoietic progenitors [5]. Increasing attention is also given to clonal hematopoiesis of indeterminate potential (CHIP), where mutations in regulatory genes (*DNMT3A*, *TET2*, *TP53*) increase susceptibility to leukemogenesis in individuals with chronic inflammatory stress [38]. Management of AML and ALL should follow standard guidelines, employing anthracycline- and cytarabine-based regimens in younger patients [1], hypomethylating agents or venetoclax in older or unfit patients [35], and consideration of allogeneic stem cell transplantation in selected cases [34].

3.4. Multiple myeloma

Multiple myeloma represents another major HM in SLE, with significantly increased risk estimates ranging from four- to ninefold higher SIRs compared with the general population [39]. A prospective cohort meta-analysis of nearly 68,000 SLE patients reported an SIR for multiple myeloma of 1.5 [3]. Pathogenesis of multiple myeloma in SLE is attributed to chronic B-cell and plasma cell stimulation, overproduction of BAFF, long-term antigen exposure including viral (EBV) factors, and potential effects of immunosuppressive therapies [40,41]. Standard treatment regimens include proteasome inhibitors, IMiDs, dexamethasone, anti-CD38 antibodies, and autologous stem cell transplantation, with special emphasis on infection prophylaxis and renal monitoring [1].

3.5. Chronic lymphocytic leukemia

For CLL, the epidemiologic correlation with SLE is less clear. Large-scale population studies show inconsistent overrepresentation, although cases of co-occurrence have been reported [40]. It has been suggested that chronic stimulation of the B-cell axis (via BAFF and BCR signaling), overexpression of survival factors (*BCL2*), and immune dysregulation may contribute to clonal expansion of mature B cells, linking chronic autoimmunity in SLE to lymphoproliferation and potential CLL development [40]. Treatment in SLE patients requires careful consideration of cytopenia and infection risks, as well as drug interactions with immunosuppressants, while standard

therapies include Bruton tyrosine kinase (BTK) inhibitors (ibrutinib, acalabrutinib) and venetoclax combined with anti-CD20 antibodies [40].

3.6. Chronic myeloid leukemia

CML does not appear to have a significantly increased risk in SLE compared with the general population, though multiple case reports describe co-occurrence [1,42]. Its development is primarily associated with the acquisition of the BCR-ABL1 fusion, while the role of the inflammatory milieu in SLE is considered indirect and secondary [40]. Treatment of CML in SLE patients relies on standard tyrosine kinase inhibitors (TKIs) such as imatinib, dasatinib, or nilotinib, with particular attention to possible masking of lupus symptoms (pleural effusions, rashes) and careful monitoring of drug interactions [43].

3.7. Myelodysplastic syndromes

Myelodysplastic syndromes (MDS) in SLE patients may arise secondarily to exposure to alkylating agents [34] or as a coexisting autoimmune disorder, where chronic inflammation, overexpression of pro-inflammatory cytokines (IL-1, TNFα), TLR activation, and bone marrow microenvironment dysfunction promote clonal hematopoiesis [5]. Mechanistically, therapy-related MDS typically presents with characteristic cytogenetic aberrations and mutations in epigenetic regulators (DNMT3A, TET2) [38]. Management should be risk-adapted according to IPSS-R/IPSS-M and include supportive care, hypomethylating agents, or allo-HSCT in high-risk patients, with parallel attention to SLE activity control and minimizing infection risks [1].

4. Hematological malignancies in SLE – cases review

SLE patients have a higher-than-average risk of developing cancer, particularly hematologic malignancies. Potential contributing factors include chronic inflammation, genetic alterations, and the use of immunosuppressants [20,33].

Nine cases of HMs in SLE were analyzed. Seven of them were females, between ages 19 and 64 (Table I). In six of those cases SLE was diagnosed before the malignancy. The most common malignancy observed was lymphoma, consistent with previous findings on the subject [10]. However, cancer incidence, preferred sites, and onset timing varied significantly in each case, making diagnosis challenging.

Table I. Summary of case reports on SLE-associated hematological malignancies

Case report	Comorbidities	Symptoms	Laboratory findings	Diagnosis	Treatment	Effect	Reference
64-year-old female	hypertension, SLE, RA, deep vein thrombosis, MZL of the conjunctiva	petechial rash, purpura and blisters on lower extremities, pitting edema tachycardia pulmonary edema AKI	neutrophilia, anemia, thrombocytosis, metabolic alkalosis, hypoalbuminemia ↑BUN, creatinine, ↑ PT, INR ↑ ESR, CRP ↑ferritin	marginal zone lymphoma presenting as MAS	high-dose steroids, cyclophosphamide (750 mg) etoposide, vincristine, and HCQ	-improved status	[26]
32-year-old female five years later	SLE	leukocytosis in routine lab tests oral mucosal ulcerations	BCR-ABL reciprocal translocation	CML SCC	Dasatinib 100 mg MMF, HCQ excision and radiotherapy	-remission -SLE symptoms remained	[27]
2.6-year-old boy five years later	N/A	fever, abdominal pain, periumbilical mass fever, malar rash, pruritus with maculo-papular scabs oral ulcers swollen cervical lymph nodes	(+) EBV ↑ CRP (+) CD20, CD79a, Ki67, PAX5, VIM, INI-1, CD34 leukopenia, anemia, thrombocytopenia (+) Coombs test (+) ANA anti-rRNP, Sm, SSA/Ro52, SSA/Ro60, SSB, dsDNA, nucleosome, histone, ribosomal ↓ C3, C4, lupus nephritis III+V	Burkitt's lymphoma SLE with features of Sjogren's syndrome	Chemotherapy, autologous stem cell transplantation GCs, HCQ, MMF	-remission	[28]

2010 19-year-old woman nine years later eleven years later	N/A	N/A polyarthritis, polyserositis, chilblains, fever, chilblain lupus, diffuse arthralgias, myalgias, and respiratory infections reduced body weight and height, hepatosplenomegaly, diffuse lymphadenopathies, malar rash, polyarthritis affecting small joints of the hands	N/A leukopenia, (+) ANA, dsDNA ↓ C3 persistent lymphopenia anemia, thrombocytosis, ↓ C3, IgA, IgG2, CD4+, CD8+ ↑ CRP, IgM, IFN–I (+) ANA	stage IIIA Hodgkin's lymphoma SLE Pneumonia MAS-like systemic inflammation, sepsis, Activated Phosphoinositide 3-Kinase-δ Syndrome 2	Chemotherapy (ABVD, IEV) autologous stem cell transplantation HCQ, azathioprine, prednisone high-dose steroids, MTX, MMF and anakinra Ig, TMP/SMX rapamycin	-remission -improved status -poor response	[29]
62-year-old woman	hypertension, ischemic heart disease epilepsy	weight loss, asthenia, pallor, headache, palpitations, fever, discolored conjunctiva, edema of lower limbs	anemia, thrombocytopenia leukopenia blastoid cells in smear 65% of myeloid blast cells (+) anti-SSA, SSB, anti-phospholipid antibodies, Coombs test	acute myeloid leukemia SLE	low dose of cytarabine Prednisone (1mg/kg/day)	-died with a septic shock	[41]

44-year-old woman	SLE, lupus nephritis, Basedow's disease, steroid diabetes, idiopathic thrombocytopenic purpura, hypertension	abdominal pain, exophthalmos, enlarged thyroid, distended abdomen	↓Hb, Htc ↑CRP, ESR, IL-2 proteinuria, leukocyturia, circumferential thickening of the jejunum with aneurysmal dilatation on CT	diffuse large B-cell lymphoma in the jejunum at stage II_{1E} which had invaded the transverse colon	colon resection cyclophosphamide, adriamycin, vincristine, and prednisone rituximab	N/A	[24]
58-year-old woman	SLE	fever back pain recurrent infection and cytopenias	↓ Hb, WBC, Tbc, AST, ALT, ALP ↑CRP, CD3+ γδ T cells (+)EBV-DNA in CD3+ γδ T cells and CD19+ B cells large lymphocytes in blood smear	γδ T-cell large granular lymphocyte (T-LGL) leukemia	recommended first-line therapy for T-LGL leukemia CyA (5 mg/kg daily)	-improved status	[42]
41-year-old woman	SLE	aphasia agraphia headache mild alopecia headache nausea	proteinuria ↓C3, C4 (+) anti-ds-DNA (+) anti-U1-RNP ↑protein in CSF ↑IL-6 in CFS brain edema and small hemorrhages on MRI brain tumor on MRI	neuropsychiatric lupus diffuse large B-cell lymphoma (DLBCL)	cyclophosphamide i.v. (500 mg) methylprednisolone i.v. (500 mg) MMF (2000 mg/day) Excision R-MPV therapy radiation cytarabine	-improved status -remission	[25]
41-year-old man	SLE	fatigue, fever, arthralgia, oral lesion,	↑ESR, CRP ↑anti-dsDNA	SLE flare-up	methylprednisolone i.v. (1 g)	-no improvement	[30]

		splenomegaly, cervical lymphadenopathy, pericardial effusion	↓complement hypercalcemia ↑pro-BNP pancytopenia osteopenia ↑mature B-cells in flow cytometry of bone marrow	nodal marginal zone B-cell lymphoma	R-CHOP chemotherapy	-remission	

This comparison highlights the heightened cancer risk associated with SLE, along with greater variability in symptom presentation and patient age. Most patients achieved remission after standard therapy, while SLE symptoms were alleviated with i.v. methylprednisolone.

5. Autoimmune hemolytic anemia

AIHA is a type of anemia caused by autoantibody mediated destruction of erythrocytes. It can be a manifestation of SLE associated with higher-than-average morbidity and mortality [44].

5.1. Risk factors

Study from a multiethnic Latin American cohort analyzes risk factors for severe AIHA in SLE patients [45]. The study finds that AIHA occurs early in the disease course, and male sex along with higher disease activity at diagnosis are predictors of its earlier onset. Hematologic abnormalities such as leukopenia, thrombocytopenia, may also indicate a higher likelihood of developing severe AIHA, although they were not statistically significant. Moreover, severe AIHA did not impact long-term damage or mortality in that cohort.

Viral infections and innate immune activation, especially via Toll-like receptors (TLRs) and inflammasomes, contribute to chronic immune activation and anemia. In SLE, anemia is linked to autoimmune hemolysis, chronic inflammation, and kidney disease, with inflammatory cytokines (IL-6, IL-1β) reducing erythropoietin (EPO) production. The presence of anti-EPO and anti-EPOR autoantibodies further exacerbates anemia in SLE patients by impairing erythropoiesis [46].

Another factor of AIHA is complement activation. The majority (90%) of SLE patients have circulating anti-erythrocyte antibodies, even without active hemolysis [44]. Additionally, 53% show complement opsonization of erythrocytes, and 29% generate the inflammatory mediator C5a (Figure 2) [44].

5.2. AIHA types and treatment

AIHA may be primary (idiopathic) or secondary to systemic autoimmune disorders, infections or malignancies. AIHA can be divided to warm (65%), cold (30%), or mixed (5%), according to the temperature at which the antibody-erythrocyte reaction occurs. Warm AIHA is caused by IgG that opsonizes RBCs at body temperature. Cold AIHA is caused by IgM that binds to RBC at temperatures below body temperature. Both can occur as idiopathic or secondary to other autoimmune diseases [47,48,49,50,51,52], infections, or malignancies. In mixed AIHA, there is the presence of both warm and cold autoantibodies and it is commonly secondary to lymphoma [53,54,55].

In warm AIHA, corticosteroids remain the first line of treatment, while for cold AIHA, steroids are often ineffective, thus rituximab is often administered [56].

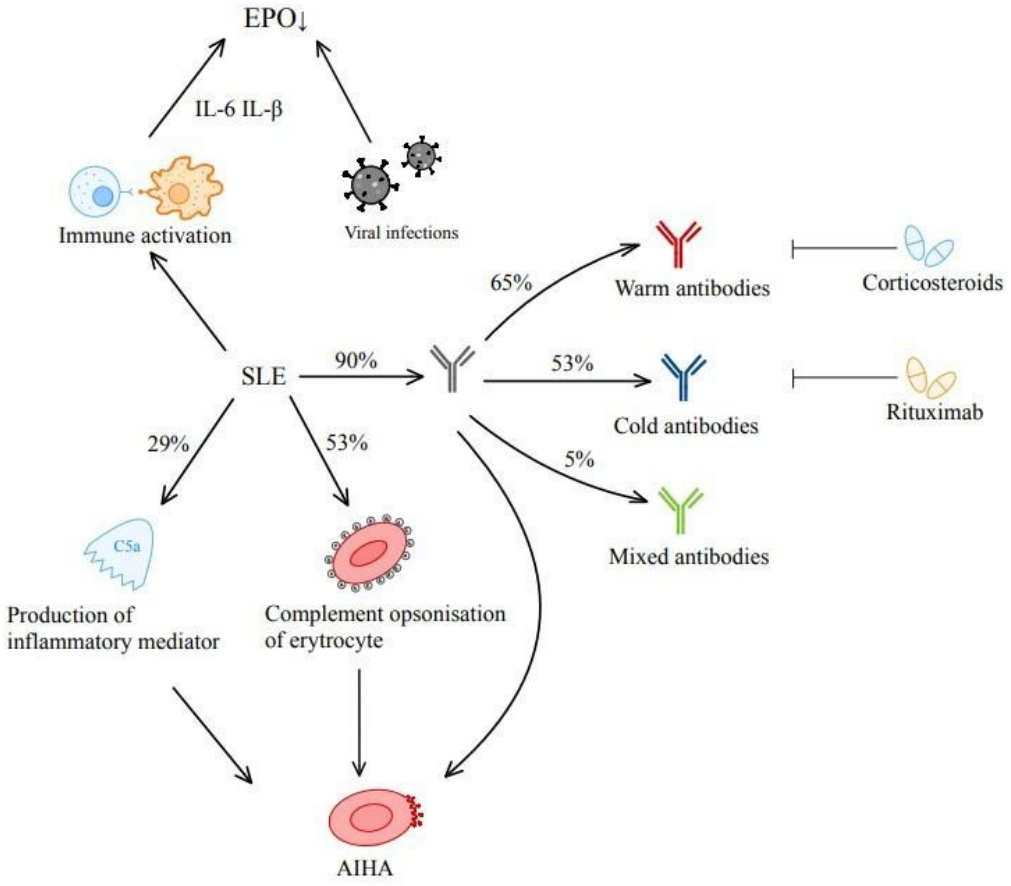

Fig. 2. AIHA-SLE-induced development

6. Novel treatment for AIHA

Corticosteroids remain the standard first-line therapy for warm AIHA, achieving response rates of approximately 80% and remission rates of 60%–70%. In contrast, corticosteroids are largely ineffective in cold agglutinin disease (CAD), where rituximab is considered the preferred first-line treatment [57].

6.1. Warm AIHA

6.1.1. B-cell targeting therapies

6.1.1.1. Phosphoinositide 3-kinase (PI3K) inhibitors

Phosphoinositide-3 kinase (PI3K) signaling is important for the survival of numerous cell types and class IA of PI3K is specifically required for the development of B cells but not for T cell development [58].

Parsaclisib

Parsaclisib is a next-generation, oral, potent, and highly selective inhibitor of the class IA PI3K enzymes that is approximately 20 000-fold selective for PI3K-δ over other isoforms. It is currently undergoing double-blind, randomized, multicenter, placebo-controlled phase 3 trial for warm AIHA [59].

Parsaclisib has shown considerable efficacy in treating B-cell malignancies. It works by suppressing B-cell proliferation, modulating regulatory T-cell homeostasis, inhibiting CD8+ T-cell maturation.

In AIHA, recent long term study conducted by Barcellini et al. [59,60] showed sustained improvements in hemoglobin levels in 25 patients with a 64% rate of partial or complete responses during weeks 6–12. However, warm AIHA presented better response than CAD or mixed AIHA. The drug was well tolerated, with 44% of patients experiencing treatment-related adverse events, most commonly diarrhea and pyrexia [57].

6.1.1.2. Bruton tyrosine kinase inhibitors

Ibrutinib

Ibrutinib is a first-in-class BTK inhibitor approved for the treatment of MCL, CLL and Waldenström's macroglobulinemia. It also shows promising results in treatment of AIHA in patients with CLL, which is in the vast majority warm AIHA. Several studies found that AIHA was suppressed during ibrutinib therapy, but worsened when ibrutinib was withdrawn [61,62,63]. Since CLL is often associated with immune dysregulation it often leads to increased risk of infection and altered immune response, as well as autoimmune cytopenia the most common of which is AIHA, occurring in 7%–10% of cases [64]. The mechanism by which AIHA is influenced by ibrutinib is yet to be understood. Interestingly, RBC-bound antibodies persist in more than half of patients during a prolonged treatment period. It may indicate probability of relapse, but most patients maintain the response.

In a mouse model in a study conducted by Rogers et al. [65] outcomes of a treatment with acalabrutinib and ibrutinib were analyzed and showed significantly greater decrease of RBC-bound antibodies in patients treated with acalabrutinib, compared to ibrutinib. However, it was not associated with faster RBC clearance.

What is more, numerous studies showed altered T-cells composition in CLL patients. Ibrutinib induces a shift in the Th2/Th1 ratio, by selectively inactivating Th2. In addition, ibrutinib treatment causes significant reduction of Th17-cells and T follicular helper cells which are and both are elevated in patients with autoimmune cytopenia. This suggests that those T cells may be involved in the pathogenesis of autoimmune cytopenia [66]. Ibrutinib may be also an effective drug in the treatment of patients with cold AIHA. In the study conducted by Jalink et al. [67] Ibrutinib has been investigated in 15 patients with primary or secondary CAD. Most of those patients were transfusion dependent and experiencing circulatory symptoms. All of them showed improvement of both hemolytic anemia and acrocyanosis.

6.1.2. CD-38 inhibitors

Daratumumab

Daratumumab is an IgGκ monoclonal antibody developed as a treatment for multiple myeloma, proved efficient in treating wAIHA, cAIHA and post-SCT AIHA.

It targets the CD38 glycoprotein, which is expressed on plasma cells, natural killer cells, monocytes, B cells, and T cells. Because CD38 is expressed on T cells, daratumumab may exert immunomodulatory effects that contribute to its therapeutic activity, since the production of autoantibodies by B cells from patients with AIHA is thought to be mediated by $CD4^+$ T cells [57]. In a prospective analysis of two patients with warm AIHA, treatment with daratumumab led to complete depletion of $CD38^+$ T cells, resulting in impaired activation and proliferation. Notably, in one patient, disease relapse coincided with the reappearance of $CD38^+$ T cells [68].

Daratumumab has primarily been studied in children and in the context of immune-mediated cytopenia following hematopoietic stem cell transplantation, and its use as monotherapy for AIHA has been rare. However, a recent study by Jalink et al. [68] analyzed outcomes in patients treated with daratumumab monotherapy, including 12 with wAIHA and 7 with cAIHA. In wAIHA, daratumumab induced rapid and durable complete hemoglobin responses in 50% of patients, with variable reductions in transfusion requirements. In cAIHA, 57% of patients achieved hemoglobin responses, often within weeks, accompanied by reduced transfusion dependence and meaningful clinical improvements, such as resolution of acrocyanosis in several cases.

The efficacy of daratumumab in post-SCT AIHA was also demonstrated by variety of different case reports [69,70,71]. For example, in the study conducted by Schuetz et al. [72] two cases of life-threatening warm AIHA post-stem cell transplantation, both successfully treated. At the same time, a third patient experienced a fatal relapse.

6.1.3. Spleen tyrosine kinase inhibitors

Spleen tyrosine kinase (SYK) is an intracellular protein tyrosine kinase involved in membrane-mediated signaling in various cells, including immune cells. It is overexpressed in T cells from patients with SLE, and its inhibition has been shown to improve T cell function by blocking Fc receptor and T cell receptor signaling [73,74].

Fostamatinib

Fostamatinib is an oral prodrug that is rapidly converted to its active metabolite R-406 in the gut. It is approved to treat adult patients with low platelet count due to chronic immune thrombocytopenia (ITP) as a second-line therapy. Moreover fostamatinib is undergoing a number of clinical trials for treatment of HMs and solid tumors [75].

Furthermore, fostamatinib is currently in Phase 3 clinical trials for primary or secondary warm AIHA. In the FORWARD trial, 90 patients with warm AIHA were randomized 1:1 to receive either fostamatinib or placebo. Although a higher proportion of fostamatinib-treated patients achieved

hemoglobin improvement compared with placebo, the difference did not reach statistical significance [57].

However, in the study conducted by Kuter et al. [76], 15 out of 24 patients with wAIHA achieved improvement.

Fostamatinib exerts its effect by inhibiting SYK, thereby suppressing both Fc receptor (FcR) and BCR signaling pathways. Upon activation, FcR associates with the FcRγ adaptor protein, which becomes phosphorylated and subsequently activates SYK. Activated SYK then phosphorylates downstream FcR substrates in phagocytic cells, leading to the phagocytosis of RBC. Moreover, activation of SYK mediates activation and differentiation of B lymphocytes into plasma cells, reducing antibody production [76].

The most commonly reported adverse effects of fostamatinib are gastrointestinal. Hypertension is another notable adverse effect, attributed to the off-target activity of fostamatinib on VEGF receptors and is a recognized consequence of SYK inhibition [77].

However, the activity of alkaline phosphatase varies depending on age, sex, hormonal status, medical condition, and diet. It binds to a wide range of protein kinase targets, for kinase insert domain receptor (KDR), which can lead to elevated blood pressure. It poses a narrow window for fostamatinib to adjust doses to achieve optimal efficacy and manage the safety at the same time [78].

Sovleplenib

Due to the limitations associated with fostamatinib, researchers sought a potent, selective, and orally bioavailable SYK inhibitor with improved selectivity and pharmacokinetic properties for the treatment of ITP, wAIHA, and other autoimmune disorders. This effort led to the development of another next-generation oral SYK inhibitor sovleplenib, which is currently evaluated in a Chinese Phase 2/3 clinical trial.

In this study 21 patients with wAIHA were analyzed, with five of them receiving a placebo. By week 24, the overall hemoglobin response rate was 67%, while the durable hemoglobin response rate was 48%. The mean FACIT-F total score- an instrument assessing self-reported fatigue and its impact on daily activities and functioning- increased at week 8 in the sovleplenib group, whereas it decreased in the placebo group.

Adverse events occurred in all patients, with 67% of them deemed drug-related. Only seven (33%) patients had grade 3 events of adverse effects, the most common of which was anemia. Other included pulmonary embolism and pneumonia [57,78].

6.1.4. Bispecific antibodies

Obexelimab

Obexelimab is a monoclonal antibody, which simultaneously binds CD19 and FcγRIIb, resulting in the down regulation of B-cells, plasmablasts, and CD19-expressing plasma cells. It is under the

investigation in a phase 2/3 clinical trial for treatment for wAIHA. Obexelimab is currently used to treat SLE and IgG4-related diseases by suppressing innate and adaptive B-cell activation pathways without destroying these immune cells.

FcγRIIb is a negative coreceptor of the BCR. When FcγRIIb and the BCR are activated together, the immunoreceptor is phosphorylated which leads to blocking downstream signaling and dampens B cell activation. In contrast, CD19 is a positive coreceptor expressed on B cells. It has intracellular regions that, once phosphorylated, recruit signaling molecules such as PI3K thereby enhancing BCR signaling and lowering the threshold for B cell activation.

Obexelimab binds with CD19 and brings FcγRIIb very close to the BCR–CD19 complex, redirecting the signaling pathway toward inhibition. When FcγRIIb is co-engaged with CD19, triggers the inhibitory signaling cascade in the B cell leads to reduced B cell activation [79]. Obexelimab is usually administered intravenously, however study conducted by Wang et al. [80] suggests that subcutaneous administration has favorable bioavailability, is well-tolerated, and showed no clinically meaningful ethnic differences in pharmacokinetics or pharmacodynamics.

6.1.5. B lymphocyte stimulator

B cell-activating factor of the tumor TNF family also known as B lymphocyte stimulator (BLyS) is a member of the TNF family, and both play an essential role in B-cell survival, maturation, and activation. BlyS production is increased in patients with WAIHA and likely involved in the pathogenesis of AIHA [81].

Ianalumab

Ianalumab is an IgG1κ monoclonal antibody of dual mechanism- it combines blockade of BLyS-R with direct lysis and depletion of B cells. Study conducted by Barcellini et al. [82] suggest that B-cell depletion from Ianalumab may exceed that of anti-CD20 monoclonal antibodies.

It is currently undergoing Phase 3 trial for treatment of wAIHA who failed at least one prior therapy. Active trials are also conducted in SLE, Sjogren's syndrome, RA, autoimmune hepatitis, and NHLs.

6.1.6. The neonatal Fc receptor inhibitor

The neonatal Fc receptor (FcRn) is also known as IgG receptor FcRn large subunit p51 and it plays a role in regulating IgG and serum albumin turnover. In fact, it binds to the Fc portion of the IgGs preventing their degradation through the endosome, which results in elongation of half-life of immunoglobulin. FcRn expression is up-regulated by pro-inflammatory cytokines, hence it is particularly active in AIHA. The blocking of FcRn by monoclonal antibodies stops IgG recycling, thereby enhancing the clearance of pathogenic autoantibodies. Nipocalimab is the only one its group to be currently undergoing phase 2/3 trial for wAIHA [83].

6.2. Cold AIHA

6.2.1. Complement inhibitors

Complement activation is one of key factors in hemolysis in AIHA, particularly in CAD, where it mediates intravascular destruction and extravascular clearance of erythrocytes. Moreover, excessive complement activation contributes to a procoagulant and inflammatory environment, increasing thrombotic risk. In CAD and WAIHA, it offers a potential option where current therapies like glucocorticoids or rituximab are often ineffective, poorly tolerated, or fail to provide lasting remission [84].

6.2.1.1. C1 inhibitors

Sutimlimab

This targeted action makes it useful for complement-mediated diseases such as cold agglutinin disease, warm AIHA, bullous pemphigoid, and antibody-mediated transplant rejection.
Sutimlimab is the first selective inhibitor of the classical complement pathway approved for CAD. It works by selectively blocking the classical complement pathway C1 and preventing complement-mediated opsonization of erythrocytes [57,85].
Two significant studies- CARDINAL and CADENZA- were conducted. The CARDINAL study was a 26-week, multicenter study with CAD patients with a recent RBC transfusion history. CADENZA was a phase III, randomized, double-blind, placebo-controlled study with patients with primary CAD without a recent history of blood transfusion.
In both trials, most patients achieved clinical benefit compared with placebo. Treatment of patients with CAD with sutimlimab reduced levels of both inflammatory markers such as IL-6, IL-10 with concurrent improvement in patients' fatigue scores. However, relapse occurs after discontinuation. Most frequent adverse events in both trials were infections and infestations, headache, dizziness, gastrointestinal disorders, fatigue, hypertension and acrocyanosis.
Moreover, both studies reported a nonsignificant 40% reduction in thrombotic events after initiation of treatment with sutimlimab, hence long-term real-world data are awaited [86].

6.2.1.2. C3 inhibitors

Pegcetacoplan

Pegcetacoplan is a subcutaneously administered C3 inhibitor, currently in an ongoing phase 3 randomized, placebo-controlled study. It was designed to prolong C3 half-life and exhibits high-affinity binding both to it and its activated fragment, C3b, inhibiting both the C3 and C5 convertases. Pegcetacoplan is used in conditions marked by excessive activation of complement including paroxysmal nocturnal hemoglobinuria, age-related macular degeneration, and some forms of glomerulonephritis.
In the phase 2 trial, pegcetacoplan shows promising activity in CAD and warm AIHA by increasing hemoglobin and controlling hemolysis. The drug was well tolerated, with diarrhea, headache, hypertension, nausea, and vitamin B12 deficiency being the most frequently reported adverse events [57,87].

7. Autoimmune hemolytic anemia in SLE patients – cases review

Nine cases of AIHA in SLE patients were analyzed, five with warm antibodies, three with cold antibodies and one with pure red cell aplasia. All patients were women, between ages 4 and 72 (Table II).

Table II. Summary of case reports on SLE-associated AIHA patients

Case report	Clinical manifestations	Laboratory findings	Hb level	Treatment	Effects	Reference
32-year-old obese Hispanic gravida	fatigue, weakness, shortness of breath on exertion, nausea, decreased food intake, dark stools for the past 2 months	(+) Coombs test, warm antibodies	4.6 g/dL	Methylprednisolone (1 mg/kg) blood transfusion	-improvement in hemoglobin levels	[47]
4-year-old girl	Epistaxis, melena fever, pallor, hepatosplenomegaly, ecchymoses, joint swelling, red spots in the parotid duct mucosa, urticarial erythema on face, left facial weakness	anemia, leucopenia reticulocytosis abnormal ↑ APTT, PT	3.9 g/dL	Prednisone p.o. (1.5 mg/kg/day) MMF (15 mg/kg/day)	-improvement in hemoglobin levels -reduction in hemolysis markers	[48]
11-year-old girl	intermittent fever, fatigue, poor appetite, weight loss (5 kg in 1.5 months) pallor, butterfly rash, thyroid enlargement (grade II)	anemia, leucopenia, (+) Coombs test, spherocytes, (+)ANA, anti-dsDNA, anti-RNP, anti-nucleosome, anti-histone ↑ T3, T4, TPOAb, TgAb	8.1 g/dL	Prednisolone (1 mg/kg/day) Leflunomide (0.3 mg/kg/day)	-improvement in hemoglobin levels -improvement in leucocytes	[48]
22-year-old woman	intermittent fever, headache, myalgia, mild rash episode, diarrhea, emesis, mild pallor, icteric sclerae, supraclavicular, cervical adenopathies, synovitis in bilateral metacarpophalangeal joints, grade II edema in the lower limbs	(+) cold agglutinin (+) antiglobulin for C3d	6.2 g/dL	Dexamethasone i.v. (40 mg./day) HCQ p.o. (200 mg/day)	-improvement in all cell lines	[49]
27-year-old woman	pallor, jaundice, fatigue, hair loss, drooping of right eye lid, pale conjunctiva	(+) ANA anti-DNA, anti-dsDNA, anti-nucleosome anti-histone	4.7 g/dL	Deltacortil (30mg/kg/day)	-improvement of hemoglobin levels -resolution of PRCA	[50]

		hypocellular marrow suppressed erythropoiesis				
72-year-old woman	Dyspnea, severe anemia, jaundice	↓ RBC, Htc ↑ TBIL, indirect bilirubin, LDH, (+) ANA, cold agglutinin, cryoglobulin, Coombs tests, HCV, HTLV-1, IgG, C3, C4 flower cells (3,5%) RBC agglutination	7.2 g/dL	oxygen on admission, Prednisolone (40 mg/day), patient refused to take warfarin, no immunosup-pressants were administered, as she was an HTLV-1 carrier	-improvement of hemoglobin levels -improved right heart overload	[55]
22-year-old woman	weakness, fatigue, intermittent body aches, nausea, headache, dizziness, chest pain, dyspnea, afebrile, tachycardia tachypnoea icterus, conjunctival pallor, jaundice	↑ LDH, bilirubin ↓ haptoglobin, reticulocytosis, RBC agglutination spherocytes reticulocytes, leukocyte–erythrocytes rosettes, (+) C3, IgG, cold agglutinin	4.9 g/dL	Prednisone (1 mg/kg) transfusion (one unit RBC) Rituximab i.v. (375 mg/m^2/week)	-improvement of hemoglobin levels	[54]
44-year-old African American woman	Arthralgias, fatigue, lightheadedness, dyspnea on exertion	(+) ANA, Sm/RNP warm antibodies, erythroid hyperplasia	3.7 g/dL	HCQ, Prednisone (1 mg/kg/day) i.v. Ig Methylprednisolone i.v. (1g/day) Rituximab i.v. (375 mg/m^2/week) Cyclophosphamide	-improvement of hemoglobin levels	[51]

				i.v. (1000 mg/21 days) All with lack of response MMF (500 mg) BID +splenectomy-partial improvement Bortezomib s.c. (1.3 mg/m^2) + MMF- long-lasting improvement		
25-year-old woman	diarrhea loss of appetite, asthenia, lethargy, weight loss fever ↑ BP periorbital edema lower limb edema palpable submandibular, cervical, and inguinal lymph nodes	thrombocytopenia ↓ haptoglobin kidney injury proteinuria, erythrocyturia, mall bilateral pleural and pericardial effusion, small volume ascites ↑TG (+) warm antibodies, ↓ C3 and C4, ↑anti-dsDNA, (+) ANA	8 g/dL (day 1) 5 g/dL (day 17) 3.9 g/dL (day 19)	Prednisolone p.o. (1 mg/kg/day) HCQ TMP-SMX+ calcium carbonate+ cholecalciferol (as prophylactic therapy) Ig i.v. Rituximab i.v. (1 g/2 week)	-improvement of hemoglobin levels -improvement in leukocytes and thrombocytes levels -improvement of kidney function	[52]

This comparison underscores the variability in clinical presentations and treatment responses of AIHA in SLE patients. While corticosteroids remain the most common treatment, additional therapies such as immunosuppressive agents and Rituximab are considered in refractory, cold or mixed-type cases. Individualized treatment approaches are essential for optimal patient outcomes.

8. Conclusions

Hematological complications in SLE represent a critical aspect of disease burden and require heightened clinical vigilance. Clinical presentation is heterogeneous, and the timing of malignancy onset may vary from the first year after SLE diagnosis to several years later, which underscores the importance of early and continuous cancer surveillance. Risk stratification should consider age at SLE onset, sex, autoantibody profiles, and treatment history. Particular vigilance is warranted when cytopenias prove refractory to standard SLE therapy, when B symptoms occur disproportionate to serologic disease activity, or when lymphadenopathy is persistent and atypical in distribution. A low threshold for bone marrow biopsy and close hematologic monitoring – especially in older male patients with long-standing immunosuppressive exposure and absent hydroxychloroquine use – may facilitate earlier diagnosis and improve outcomes.

AIHA is another clinically significant hematologic manifestation of SLE, which may present as warm, cold, or mixed type, and its severity can range from mild, asymptomatic anemia to life-threatening hemolysis. Early identification of AIHA is crucial to prevent severe anemia, organ damage, and associated complications. Monitoring hematologic parameters regularly in SLE patients, particularly those with active disease or other cytopenias, facilitates timely diagnosis and intervention.

Recent advances highlight the growing importance of targeted therapies addressing both B-cell dysregulation and complement activation in AIHA. Agents such as PI3K, BTK, and SYK inhibitors, anti-CD38 antibodies, bispecific antibodies, FcRn blockers, and complement inhibitors show encouraging efficacy and acceptable safety profiles, particularly in steroid-refractory disease. These findings may significantly influence future treatment algorithms and improve long-term patient outcomes.

The concurrent use of DMARDs and hematologic malignancy treatments in SLE patients requires careful individualization, as direct evidence remains scarce. Therapeutic overlap between the two disease areas -most prominently rituximab and cyclophosphamide - may allow simultaneous management of SLE and associated lymphoma. In contrast, methotrexate, mycophenolate mofetil, and azathioprine should generally be discontinued during treatment for active malignancy. Hydroxychloroquine remains safe to continue throughout, while newer biologics such as belimumab and anifrolumab, as well as JAK inhibitors, should be deferred until oncologic remission is achieved.

HMs and AIHA illustrate the diverse clinical spectrum of hematologic complications in SLE. Their heterogeneous presentation, overlapping risk factors, and potential for severe outcomes highlight the necessity of early recognition, individualized treatment strategies, and close follow-up. Future prospective studies are needed to further define risk factors, elucidate molecular mechanisms, and optimize diagnostic and therapeutic algorithms, with the ultimate goal of reducing morbidity and improving long-term outcomes in this high-risk population.

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Authors' contribution

Study design – J. Mastalerz, M. Szmyrka

Data collection – K. Siemek, K. Wojakowicz, Z. Rzepkowska, O. Kubiś

Manuscript preparation – K. Siemek, K. Wojakowicz, Z. Rzepkowska, O. Kubiś, J. Mastalerz, M. Szmyrka

Literature research – K. Siemek, K. Wojakowicz, Z. Rzepkowska, O. Kubiś

Final approval of the version to be published – K. Siemek, K. Wojakowicz, Z. Rzepkowska, O. Kubiś, J. Mastalerz, M. Szmyrka

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