Lupus-like manifestations in MDS/CMML: evidence for clonal origin and therapeutic implications

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Key points:

Question: What are the clinical characteristics of lupus erythematosus (LE) associated with MDS/CMML, and is there evidence that inflammatory manifestations may be driven by clonal myeloid cells?

Findings: In this cohort study of patients with LE associated with MDS/CMML, patients showed a distinct phenotype compared with idiopathic LE, with limited response to standard treatment, notable improvement with clone directed treatments, and evidence of clonal involvement in skin lesions.

Meaning: MDS/CMML-associated lupus-like manifestations represent a distinct syndrome driven by clonal hematopoiesis, warranting early hematologic evaluation and consideration of clone-directed therapy. MDS/CMML cutis should be considered in refractory CLE or SLE in older patients.

Social Media Post

MDS/CMML-associated lupus displays an atypical phenotype, with older age, male predominance, less renal/articular disease and fewer antiantibodies. The findings support clonal inflammation, and treatments targeting the clone have produced positive results.

Abstract

Importance: Immune-mediated inflammatory diseases are rare but increasingly reported among patients with myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML). Systemic lupus erythematosus (SLE) and cutaneous lupus erythematosus (CLE) associated with MDS/CMML have been rarely described, with atypical features and refractory disease.

Objective: To provide a comprehensive description of the phenotype and therapeutic responses of lupus erythematosus (LE) associated with MDS/CMML and to compare them with idiopathic LE.

Design: Retrospective case-control study conducted between 1975 and 2023 with median follow-up period of 4.5 years [1-31].

Settings: Nationwide multicenter study.

Participants: Twenty-four patients with MDS/CMML who either fulfilled classification criteria for SLE (n=19) or had skin lesions diagnosed as CLE (n=5) were included. For MDS/CMML-SLE, a 2:1 case-control study was conducted with idiopathic SLE (n=38). Clinical features, centralized skin histopathology, and targeted next-generation sequencing (NGS) were analyzed.

Results: A total of 24 patients were included: 19 with SLE and 5 with CLE. Median age at diagnosis was 65 years [range 32-85], and 9 patients (46%) were females. Cutaneous involvement was the most common manifestation of LE (n=17, 71%). Chilblain lupus was predominant subtype (n=6, 35%). Compared with idiopathic SLE, patients with MDS/CMML-associated LE were older (65 [32–85] vs 23 [11–55]; $p<0.001$), more frequently males (54% vs 8%; $p<0.01$), had less renal (10% vs 71% $p<0.001$) and articular involvement (36% vs 97% $p<0.001$) and reduced anti-dsDNA positivity (32% vs 76% $p=0.001$). The underlying hematologic diseases included MDS (n=16, 66%) and CMML (n=8, 34%), with 92% classified as lower-risk (R-IPSS ≤3.5). Centralized histopathological review reclassified 50% of skin biopsies as MDS/CMML-cutis. Identical myeloid mutations were detected in blood and skin in 6/8 cases, supporting a clonal inflammatory process. Standard LE therapies were often poorly effective, while clone-directed therapies (azacitidine or allo-HSCT) led to parallel hematologic and LE responses in 5/7 patients.

Conclusion and relevance: MDS/CMML-associated lupus like manifestations represents a distinct entity mimicking SLE or CLE and characterized by clonal inflammation rather than classical autoimmunity in most

87 cases. Early recognition is important, as treatment may require clone-targeting therapies rather than conventional
88 LE therapy.

Introduction

Myelodysplastic neoplasms (MDS) are clonal hematopoietic stem cell disorders characterized by cytopenia and morphologic dysplasia, while Chronic myelomonocytic leukemia (CMML) is a myelodysplastic/myeloproliferative neoplasm frequently exhibiting features similar to classical MDS and accompanied by sustained peripheral blood monocytosis (1). Immune-mediated inflammatory diseases (IMIDs) are observed in 10-25% of cases (2, 3), most frequently in IPSS low-risk patients (5).

In contrast to idiopathic forms, IMIDs associated with MDS/CMML often exhibit atypical features: older age, male predominance, absence of antibodies, and a refractory disease course. While corticosteroids are effective in approximately 80% of cases, relapse or steroid dependence occurs in about half of patients (4).

The pathogenesis of these associations remains unclear. Hematopoietic abnormalities may promote the development of IMIDs through the expansion of pathological clones infiltrating peripheral tissues, or conversely, chronic immune activation might drive clonal hematopoiesis and dysplasia (5). Some studies have suggested a shared genetic susceptibility involving somatic mutations in myeloid and lymphoid progenitors, which may underlie both IMIDs and hematologic disorders (6).

Our group and others specialists in the field have identified a clonal relationship between MDS/CMML and IMIDs particularly in the skin (7, 8, 9), leading to the description of "MDS cutis", defined as infiltration of the skin by dysplastic immature clonal myeloid cells. This concept has been further substantiated by the identification of VEXAS syndrome (10), where identical somatic *UBA1* mutations were found in both hematopoietic cells and skin lesions (10).

Lupus erythematosus (LE) is a rare autoimmune disease ranging from skin limited cutaneous lupus erythematosus (CLE) (11), to systemic lupus erythematosus (SLE) (12). Notably, patients with SLE show an increased incidence of MDS (13).

Some cases of MDS/CMML-associated LE have been reported, highlighting advanced age of patients and the refractory nature of the disease (14). However, no study has specifically characterized their clinical and immunological spectrum, nor treatment options. Similarly to other IMIDs, MDS- or CMML-associated LE may be related to clonal infiltration by pathological myeloid clones. However, this hypothesis was not supported by pathological and molecular analyses in a case report (14).

The objectives of the study were 1/ to comprehensively characterize the clinical, immunological, pathological, and molecular features of LE (either SLE or CLE) occurring in the setting of MDS or CMML, 2/ to compare them with idiopathic SLE, and 3/ to evaluate treatment responses.

Patient and Methods

Study design

This retrospective, nationwide multicenter study was conducted across 13 tertiary care hospitals and included patients diagnosed with LE, either CLE or SLE associated with MDS or CMML between 1975 and 2023. Cases were identified through a call for cases within the following research groups of the "Medicine INterne, HEMatologie et Oncologie (MINHEMON)" club, the "Etude des Maladies Systémiques en Dermatologie (EMSED)" group and the "Société Nationale Française de Médecine Interne (SNFMI)". Data were collected retrospectively with a standardized case report form, in adherence to STROBE guidelines.

Patients were included if they had 1/ a diagnosis of MDS or CMML according to the 2022 World Health Organization (WHO) criteria (15) 2/ a diagnosis of SLE fulfilling Systemic Lupus International Collaborating Clinics (SLICC) criteria (16) or a diagnosis of CLE based on clinical and pathological features (17).

Patients were excluded if they had a documented diagnosis of VEXAS syndrome (18), therapy-related MDS/CMML (azacitidine), drug-induced lupus, or if there was an interval of more than ten years between the diagnoses of MDS/CMML and LE.

A non-matched control group of 2:1 with idiopathic SLE (n=38) was randomly selected from a retrospective monocentric cohort provided by the immunology department of a tertiary care center (19). These controls were independent from the MDS/CMML-lupus cohort, and no patient reclassified during centralized pathology review originated from this control group. Comparative analyses were performed with MDS/CMML-associated SLE patients according to SLICC criteria at the time of diagnosis. The patients were not deliberately matched, as our methodological choice was to emphasize phenotypic differences between these two groups, rather than compare two artificially aligned populations **(Supplemental Figure 1).**

Data collection and definitions

We collected clinical, biological, cytogenetic, molecular, histological, and therapeutic data for each patient. The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) (20) was used to evaluate LE activity. CLE subtypes were classified based on Gilliam and Sontheimer classification (17). For MDS/CMML, the Revised-International Prognostic Scoring System (IPSS-R) was utilized to stratify patients into lower- and higher-risk groups, with a 3.5-point cut-off for R-IPSS (25).

Histopathological review

A centralized review of skin biopsies was conducted by 3 pathologists specialized in cutaneous manifestations of MDS/CMML (8, 21, 22) and CLE. Biopsies were classified in CLE, myelodysplasia cutis (MDS-cutis) (8, 9), Kikuchi-like inflammatory pattern (KLIP) in CLE (23) and plasmacytoid dendritic cell (pDC) dermatosis (24), taking into account the composition of the infiltrate, the cytological appearance and the immunophenotype of cells. Distinctions were made between mature pDC CD123+ TCF4+ MPO- found within the dermal lymphocytic infiltrate in CLE and plasmacytoid dendritic cell dermatoses; histiocytes CD123+ MPO+ TCF4- found in KLIP mixed with nuclear debris; and immature atypical myeloid cell CD68+ CD163+ MPO+ infiltrates found in MDS-cutis that can also express few CD123 and TCF4 (25, 26, 27). Presence of a purely blastic infiltrate was excluded on the basis of CD34, CD56, CD117 and Ki67 immunophenotyping (28).

Molecular analysis

Next-generation sequencing (NGS) data from targeted myeloid panels was performed on peripheral blood (n=14) or bone marrow (n=5) samples. These analyses were not centralized. A total of 18 genes that are commonly mutated in myeloid malignancies were identified, allowing identification of clinically relevant genetic alterations **(Supplemental Table 1).**

Outcome definitions

LE response was categorized as: 1/ complete response (CR) : disappearance of clinical and biological manifestations (SLEDAI-2K=0) (29), 2/ clinical response: resolution of clinical manifestations (clinical SLEDAI-2K, cSLEDAI-2K=0) with persistent biological activity (decreased C3 levels and/or positive anti-dsDNA antibodies).

Hematological responses were evaluated in accordance with the IWG 2018 (30) and IWG 2023 (31) criteria when hematological treatment was administered. Acute myeloid leukemia (AML) was characterized by a total myeloid blast count that exceeds 20%.

Statistical analysis

Descriptive statistics included frequency (percentage) for the categorical variables and the median [range] for the quantitative variables. Conventional Fisher's exact or Chi square tests were used as appropriate to compare categorical variables, and the Mann Whitney test was employed to compare continuous variables. Statistically significance was set as $p<0.05$. Statistical analyses were performed using JMP v17. Figures and graphs were

created using GraphPad Prism (GraphPad, San Diego, CA, USA) and Biorender (*BioRender.com*. Toronto, Canada).

The study complied with Good Clinical Practice and the Declaration of Helsinki, with IRB/Ethics Committee approval (IRB 00006477, CER-2022-194) and exemption from written consent.

Results

Patient clinical and immunological features

Patient characteristics are presented in **Table 1.** A total of 24 patients with MDS/CMML-associated LE were included: 19 with SLE and 5 with isolated CLE. Median age at diagnosis was 65 years [range 32-85], and 9 patients (46%) were females. LE was diagnosed before MDS in 10 patients (42%), concomitantly in 10 patients (42%) (less than 3 months between two diagnosis), and after MDS diagnosis in 4 patients (17%).

Cutaneous involvement was the most common manifestation of LE, affecting 17 patients (71%). Chilblain CLE was the predominant subtype (n=6; 35%), typically localized to the fingers and ears (n=3/6), followed by discoid CLE (n=5; 29%), subacute CLE (n=5; 29%), acute CLE (n=4; 24%), and tumid CLE (n=4; 24%) **(Figure 1)**. Articular involvement was observed in 9 patients (38%), mostly presenting as inflammatory arthralgia without synovitis. Serositis was observed in 7 patients (29%), including pleuritis in 5 and pericarditis in 2. Renal involvement was rare, with 2 lupus nephritis (class III and IV). The median SLEDAI-2K score at diagnosis was 9 [5-16]. One patient presented with antiphospholipid syndrome and arterial thrombosis, and another autoimmune hemolytic anemia. The mean corpuscular volume (MCV) at LE diagnoses was 94 fL [72 -105].

Antinuclear antibodies (ANA) were positive in 20 patients (83%), including all SLE patients, with a median titer of 1:160 [1:160 – 1:1280]. Four patients had no antibodies (CLE). Anti-dsDNA antibodies were present in 6 patients (25%), and decreased C3 level was found in 10 patients (43%). Other autoantibodies included anti-Sm (n=1), anti-SSA (n=2), anticardiolipin (n=3), anti-B2GP1 (n=2), and lupus anticoagulant (n=1).

Hematologic characteristics

MDS was identified in 16 patients (66%), including 8 without excess blasts and multilineage dysplasia, and 4 with increased blasts. CMML was diagnosed in 8 patients (33%), predominantly CMML-0 (n=5) (**Table 1)**.

At the time of MDS/CMML diagnosis, anemia (Hb<10g/dL) was observed in 11 patients (46%) with MCV of 92.5 fL [72–103]; neutropenia (absolute neutrophil count (ANC) <1G/L) in 8 patients (33%), and thrombocytopenia (platelets <100 G/L) in 7 patients (24%). The median monocyte count in CMML patients was 1,95 G/L [1.6– 2.5]. Bone marrow blasts ≥5% were observed in 4 patients (median 6.5% [6-18]).

Cytogenetic analysis was available for 22 (92%) patients. A normal karyotype was observed in 13 cases (59%). Abnormalities included del 20q (n=6), del5q (n=1), del11q (n=1), and one case with both del(11q) and del(9q).

NGS was performed in 19 patients (79%), using targeted myeloid panels. The most frequently mutated genes were *TET2* (n=8; 42%), *KRAS* (n=7; 37%), *ASXL1* (n=5; 26%), *SRSF2* (n=4; 21%) and *CBL* (n=3 ;16%). *TET2*, *SRSF2*, *CBL*, *TP53* were the most common mutations in MDS patients, whereas *KRAS*, *ASXL1*, and *TET2* predominated in CMML**.** Details are presented in **Supplemental Figure 2.** *UBA1* was negative in 16/24; not tested in others as VEXAS was not suspected (young women without inflammatory syndrome).

Most patients (n=22; 92%) had low-risk MDS/CMML, as defined by an IPSS-R score ≤ 3.5.

Skin biopsy findings in MDS/CMML-associated LE patients:

A total of 22 skin biopsies of LE lesions taken from 12 patients (71%) were available for centralized review. Detailed results are presented in **Supplemental Table 2.**

Histopathological features included dense dermal lymphocytic infiltrates with perivascular and perieccrine involvement in all cases (n=12; 100%), interface dermatitis in 8 patients (67%), and dermal mucin deposition in 5 (42%). No vasculitis was found. Direct immunofluorescence was performed in 5 cases; none showed a positive lupus band test.

After centralized review, the most common diagnosis was MDS cutis found in 6 patients (50%) (**Figure 2)** showing a dense, perivascular and perieccrine dermal infiltrate, comprising a minority of reactive CD3+ T lymphocytes and predominantly clusters of atypical, immature, non-blastic myeloid cells expressing CD68 and MPO with reniform irregular and hyperchromatic nuclei. These clusters were sometimes accompanied by mature neutrophils and often by leukocytoclasia. Ki67 was low (<10%).

Four patients (30%) showed CLE with clusters of histiocytes with a mature pDC phenotype (CD123+, TCF4+ MPO-). Only one (8%) had KLIP: histiocytes CD163+ CD123+ MPO+ TCF4- mixed with nuclear debris. One patient (8%) showed an appearance of pDC dermatosis with predominant cells CD123+, TCF4+ MPO- cells.

A targeted myeloid panel NGS was performed on skin biopsy samples from 8 patients with MDS, including one who later progressed to CMML-1, although the biopsy was performed at the MDS stage. Identical myeloid mutations were detected in the peripheral blood and skin samples of the 6/8 patients (Supplemental Table 2). Four of these cases had pathological lesions reclassified as MDS-cutis. One patient reclassified as having pDC dermatosis shared a clonal mutation in both tissues. Similarly, one patient who was reclassified as having a

chilblain lupus lesion with shared clonal mutations in both tissues, albeit with a low Variant Allele Frequency (VAF) in the skin sample. In contrast, no mutations were detected in the skin biopsy from the KLIP case (**Supplemental Table 2.)**.

Comparison between MDS/CMML-associated SLE and idiopathic SLE

We carried out a case control analysis comparing the 19 patients with MDS/CMML-associated SLE according to SLICC criteria and 38 patients with idiopathic SLE.

In univariate analysis, patients with MDS/CMML-associated SLE were significantly older (median 65 [32–85] vs 23 [11–55]; p<0.001), more frequently males (54% vs 8%; p<0.01), had less renal (10% vs 71% p<0.001) and articular involvement (36% vs 97% p<0.001) than those with idiopathic SLE. This group also showed lower ANA titers (median 1:320 vs 1:1280; p<0.001), reduced anti-dsDNA positivity (32% vs 76% p=0.001), and less frequently decreased C4 levels (42% vs 76% p=0.008) **(Supplemental Table 3).**

Treatment and outcomes

Median follow-up period was 4.5 years [1-31], during which 7 patients (30%) died: 2 from sepsis, (one while azacitidine treatment), 2 from hematological complications (AML transformation with leucostasis, and CMML-2 evolution), one succumbed to CNS bleeding (severe thrombocytopenia), one from cardiac failure, and one from an unknown cause.

For LE treatment, 15 patients (63%) received hydroxychloroquine (HCQ) alone, at a dose of 5 to 6 mg/kg/day. Among them, 4 patients (27%) achieved CR, 2 (13%) achieved a clinical response, and 9 (60%) showed no response. Twelve patients (50%) received HCQ in combination with oral corticosteroids (median dose 1mg/kg/day). Among them, 6 (50%) achieved CR, 3 (25%) clinical response, and 3 (25%) showed no response. Three patients received Rituximab, 2 achieved CR (66%), and one showed no response (33%). Other treatments included methotrexate (n=3), azathioprine (n=1), belimumab (n=1), without complete response. One patient with a del20q karyotype had a complete response to lenalidomide. All systemic treatment responses are detailed in **Figure 3**. Regarding topical treatments, corticosteroids were used by 13 patients, resulting in CLE response in 2 cases (15%). Five patients received topical tacrolimus, but there was no response.

Overall, two patients progressed to AML, one to MDS with increased blasts 2 (MDS-IB2), and one from CMML-0 to CMML-1. Seven patients (29%), all of whom had active LE features, received specific treatment for MDS/CMML. One patient was treated exclusively for refractory CLE and achieved lupus CR following azacitidine

treatment **(Supplemental Figure 3)**. One patient underwent allogeneic stem cell transplantation (allo-HSCT), with complete hematological and lupus CR. This patient had no cutaneous manifestations and has not developed any features of graft-versus-host disease (GVHD) to date. One patient was treated with azacytidine (AZA) and venetoclax, resulting in a complete cytologic response and lupus CR. Of the 5 patients who received AZA, 2 achieved LE CR, with a partial hematological response, one achieved a clinical LE response with stable hematological disease, and 2 had hematological progression without LE improvement (**Table 2)**.

Discussion

This nationwide multicenter study highlights a distinct LE phenotype in the context of MDS/CMML, suggesting that these patients should rather be classified as having lupus-like disease. Compared with patients with idiopathic SLE, those with MDS/CMML-LE were older and predominantly male, exhibiting a distinct clinical and immunological profile. CLE involvement was characterized by a high prevalence of chilblain lupus, while renal manifestations were rare. These findings are consistent with previous reports of IMIDs occurring alongside clonal hematopoiesis or myeloid neoplasms, including neutrophilic dermatoses, relapsing polychondritis, and VEXAS syndrome (32, 2, 3).

A key finding of this study is the demonstration that LE-like manifestations in MDS/CMML may be caused by clonal infiltration rather than classical autoimmunity. While MDS/CMML-associated LE frequently exhibits classical histological features of CLE, our centralized pathological review led to the reclassification of 6 out of 12 patients as having MDS/CMML-cutis, due to presence of non-blastic dysplastic immature myeloid cells. In 4 cases presenting with MDS-cutis, one with pDC dermatosis and one with chilblain lupus, the same myeloid mutations identified in peripheral blood were also present in the skin **(Supplemental Table 2)**. This provides molecular confirmation of clonal myeloid infiltration. It extends prior observations showing that neutrophilic dermatoses, classified as Sweet syndrome, or histiocytoid variants rich in mononuclear cells with histiocytic appearance with folded or reinform nucleus, may represent cutaneous expression of clonal myeloid diseases such as MDS, CMML, or VEXAS syndrome where cellular atypia are more obvious (10, 8, 9).

These findings may have important therapeutic implications. Classical LE therapies (HCQ and corticosteroid) were only partially effective, whereas hematologic therapies targeting the clonal disease led to clinical improvement. Among six patients receiving azacitidine, three achieved a lupus CR and one clinical response. Another patient treated with allogeneic hematopoietic stem cell transplant achieved complete response of both LE and hematologic disease.

Interestingly, most patients had low-risk myelodysplastic syndromes according to the IPSS-R, which may explain why hematologic therapies were not used more widely. In selected patients, hematologic treatments were initiated despite the absence of a formal hematologic indication, based primarily on the severity or refractoriness of LE-like manifestations. This suggests that, in atypical or treatment-resistant LE occurring in the context of MDS or CMML, clinical features of LE may help justify expanding the indication for hematologic therapy. These results

align with the increasing awareness that clonal autoinflammatory syndromes frequently require clone-directed interventions, as immune-directed therapies alone may be ineffective when systemic inflammation is driven by dysregulated hematopoietic cells (33, 34, 35).

This study has several limitations. Its retrospective design may have led to incomplete data and heterogeneity in management strategies. Moreover, it is possible that additional mutations, not detected by our targeted myeloid NGS panel, may have been acquired and could account for some of the clinical presentations. The sample size was limited. Nevertheless, the central review of skin biopsies and use of paired NGS on skin and blood samples strengthen the validity of the clonal hypothesis.

In conclusion, MDS/CMML-associated LE represents a distinct inflammatory syndrome, likely mediated by clonal hematopoietic cells rather than classical autoimmunity. Rather than having true idiopathic LE, these patients likely have a clonal inflammatory phenotype mimicking LE, that may be driven by dysregulated myeloid clones infiltrating target tissues such as the skin. The improvement of both cutaneous and systemic manifestations following hematologic treatment suggests that extracutaneous features may also be clone-dependent, even in the absence of histological confirmation. Recognizing this entity is essential to avoid misdiagnosis and therapeutic failure. In patients with atypical or treatment-resistant lupus—especially in older adults, men, with chilblain CLE or those with cytopenia or monocytosis—a myeloid neoplasm should be systematically considered. Conversely, the presence of LE-like features in MDS/CMML patients should prompt careful clinical and histological review to analyze the cell populations in the skin precisely. Further research is needed to refine diagnostic criteria and establish whether the early use of clone-targeting agents, such as azacitidine, may improve outcome even in the absence of conventional hematologic indications.

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Author contribution:

JC, FC, AMe, VJ designed the study.

JC gathered data.

FC conducted statistical analysis.

JC, VJ, PF, LPZ, OF, JH, RB, ADV, PJ, VG, EBe, EBr, VL, TM, JDB, MINHEMON group, EMSED group included patients.

MB, PM, PR and EZ performed anatomopathological reviews

PH performed biomolecular analysis.

ZA, AMa, PB gathered idiopathic lupus data.

JC, FC, VJ, PM, PF and MB wrote de manuscript.

All authors read and approved the final version of the manuscript.

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Access to data and data analysis:

Jeanne Chauffier had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement

Study data will be made available upon reasonable request to the corresponding authors, with the exception of genetic data, which cannot be shared due to confidentiality restrictions.

Meeting presentation

This project results will be presented at the Journées Dermatologiques de Paris on December 4.

Figures and Tables:

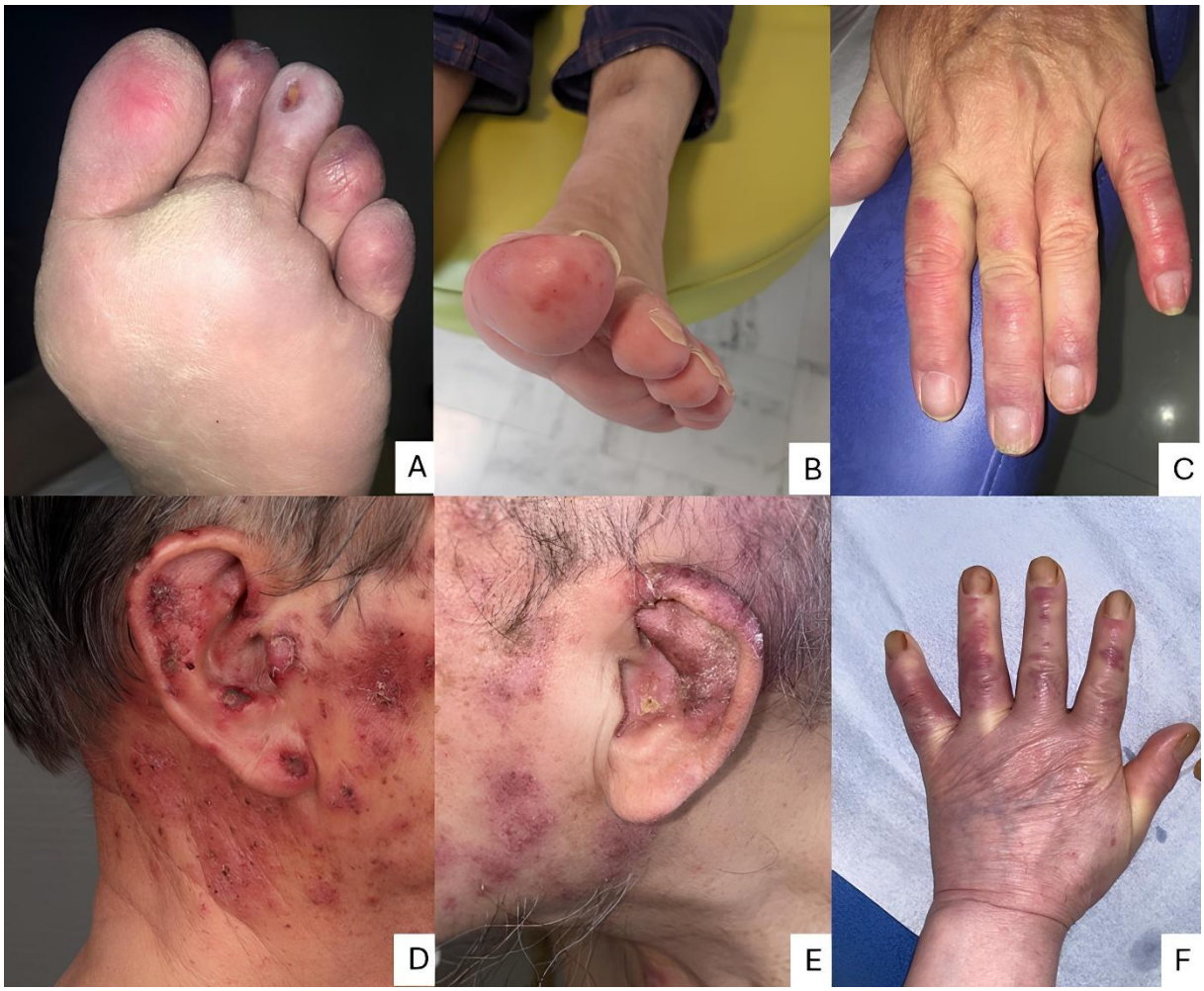

Figure 1. Cutaneous lesions in MDS/CMML-associated lupus erythematosus

A, B: Pedal pulp lesions of chilblain lupus type, with an ulcerated lesion of the third toe shown in Figure A, in conjunction with associated cyanotic lesions, C, F: Digital lesions of chilblain lupus type, accompanied with confluent band-like lupic papular lesions on the dorsal hands, sparing the extensor surfaces of the interphalangeal joints. D, E: Chilblain lupus involving the auricular pavilion.

Abbreviations: CMML: chronic myelomonocytic leukemia; MDS: myelodysplastic syndromes

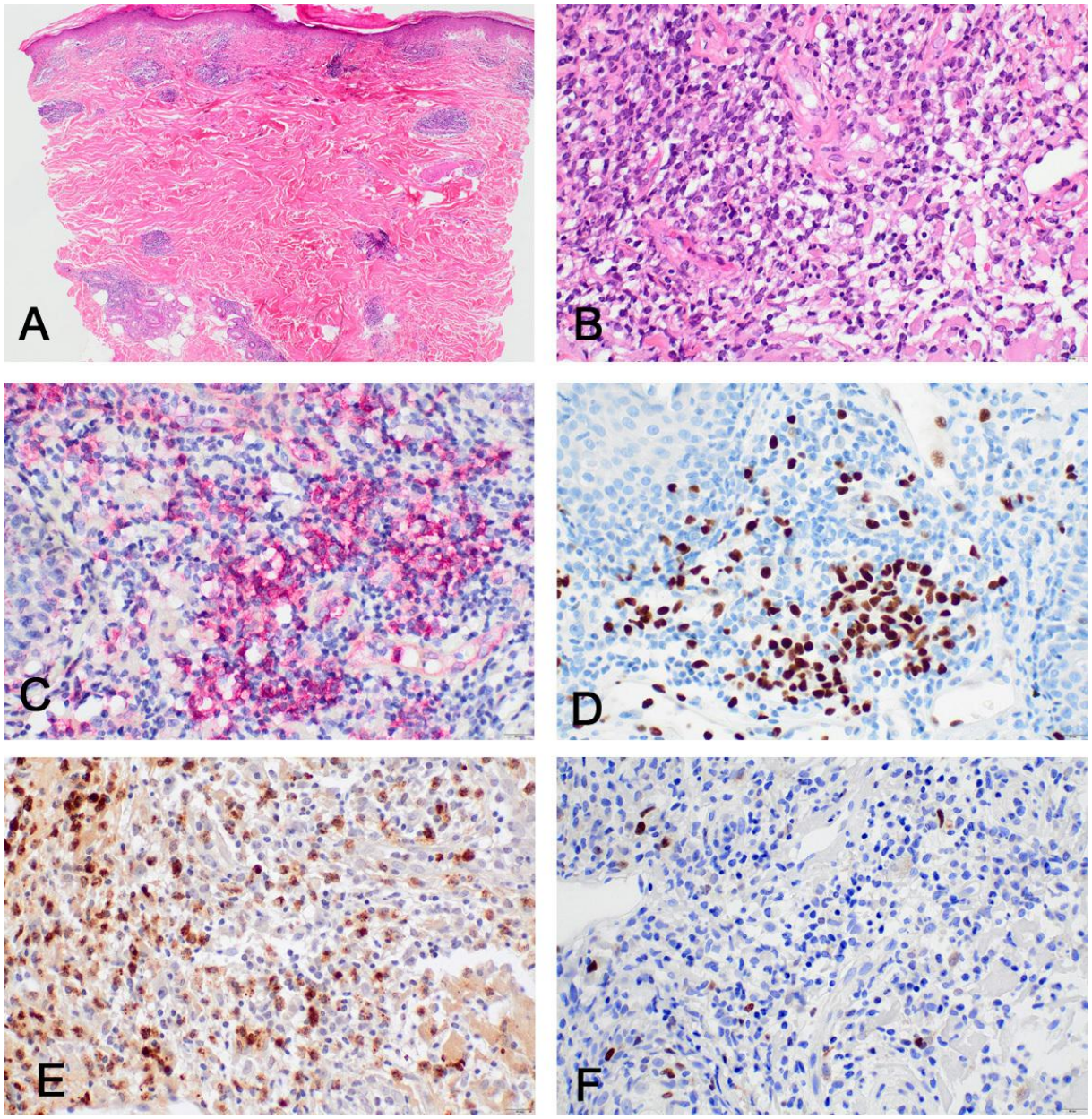

Figure 2. Histopathological and immunohistochemical findings in a patient with MDS cutis.

A, B: Hematoxylin-Eosin-Saffron (HES) staining of the skin biopsy reveals a dermal inflammatory infiltrate with dense lymphocyte infiltrate including perivascular infiltrate and peri-eccrine infiltrate, with immature precursors; atypical mononuclear cells are observed with reniform irregular and hyperchromatic nuclei (original magnifications x40 (A) and x400 (B)). C, D, E Immunohistochemical analysis revealed that these atypical cells expressed CD123 (C), few TCF4 (D) and/or MPO (E) with a low Ki67, which supports the diagnosis of MDS cutis (original magnifications x400 (C, D, E, F).

Abbreviations: CMML: chronic myelomonocytic leukemia; MDS: myelodysplastic syndromes, MPO: myeloperoxidase.

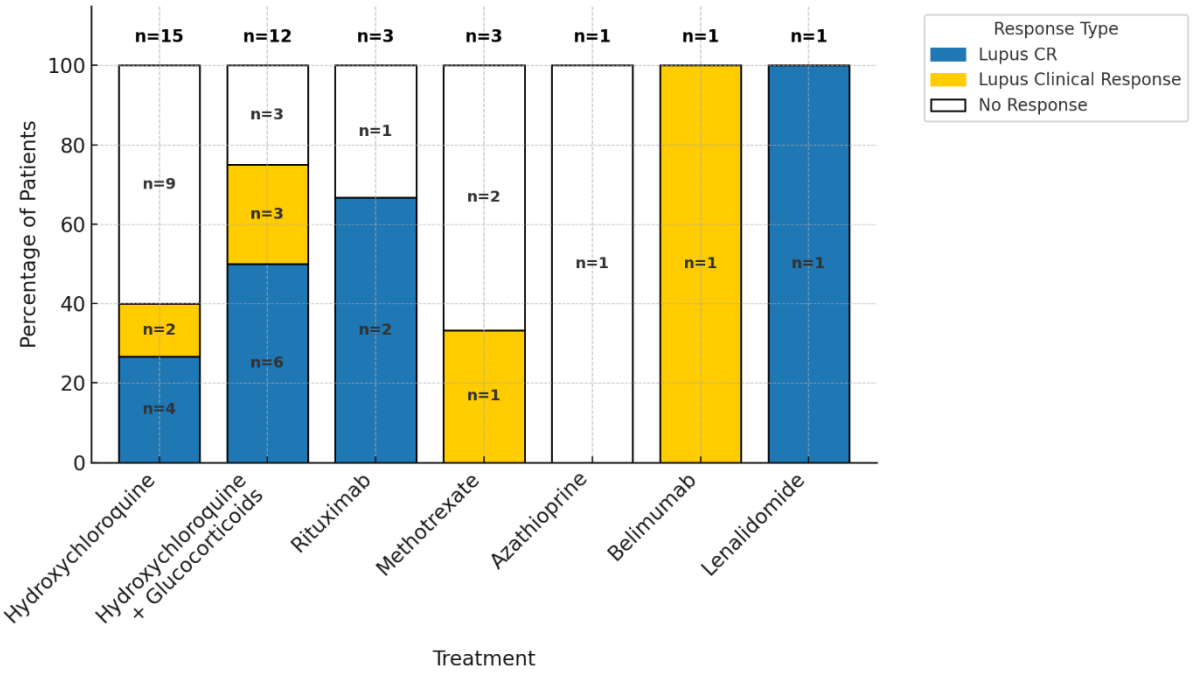

Figure 3. Efficacy of lupus therapies in MDS/CMML-associated LE.

Bar plot showing LE responses by treatment strategy. Outcomes are categorized as complete response (blue), clinical response (yellow), or no response (white). Number of patients (n) is indicated above each bar.

Abbreviations: Lupus CR: lupus complete remission. CMML: chronic myelomonocytic leukemia; MDS: myelodysplastic syndromes.

	MDS/CMML associated LE (n=24)
Demographics	
Female / Male	11 (46) / 13 (54)
Age at LE onset	66.5 [32 – 85]
Lupus features	
Cutaneous involvement	17 (71)
Specific LE features:	15 (63)
Chilblain CLE	6
Discoid CLE	5
Subacute CLE	5
Acute CLE	4
Tumid CLE	4
KLIP	2
Articular involvement	9 (38)
Serositis	7 (29)
Renal involvement	2 (9)
Auto-antibodies	
ANA positivity	20 (83)
Titer	160 [160 – 1280]
Anti-dsDNA positivity	6 (25)
Anti-SSA	3 (13)
Anti-SSB	2 (8)
Anti-nucleosome	3 (13)
Anti-RNP	2 (8)
Anti-Sm	2 (8)
Anti-Cardiolipin	2 (8)
Anti-B2GP1	3 (13)
Lupus anticoagulant	1 (4)
Decreased C3 levels	10 (43)
Decreased C4	9 (38)
Hemolytic autoimmune anemia	1 (4)
Antiphospholipid syndrome	1 (4)
SLEDAI-2K at LE diagnosis	9 [5-16]
Hematological features at MDS/CMML onset	
Hemoglobin (g/L)	10.8 [5.2 – 14.3]
Platelets (G/L)	130 [31 – 457]
Neutrophils (G/L)	1215 [60 – 12000]
Monocytes (G/L) in CMML patients (n=8)	1950 [1600 – 2500]
Dysgranulopoiesis	13 (54)
Dyserythropoiesis	9 (38)
Dysmegakaryopoiesis	12 (50)
Bone marrow blasts (%)	3 [0 - 18]
Abnormal marrow cytogenetics	
Del20q	6 (25)
Other	3 (13)
WHO 2022 classification of hematological features at LE diagnoses	
MDS	16 (67)
MDS-LB with multiple lineage dysplasia	8 (30)
MDS-LB with single-lineage dysplasia	2 (9)
MDS-LB unclassifiable	2 (9)
MDS with excess blasts 1	4 (17)
CMML	8 (33)
Chronic myelomonocytic leukemia 0	5 (22)
Chronic myelomonocytic leukemia 1	2 (9)
Chronic myelomonocytic leukemia 2	1 (4)
Lower-risk MDS/CMML (IPSS-R $\leq$ 3.5)	22 (92)

Table 1. Characteristics of patients with MDS/CMML-associated lupus erythematosus

Data are presented as n (%) or median [range], as appropriate.

Abbreviations: ANA: antinuclear antibodies; APS: antiphospholipid syndrome; CLE: cutaneous lupus erythematosus; CMML: chronic myelomonocytic leukemia; MDS: myelodysplastic syndromes; MDS-LB: myelodysplastic syndrome with low blasts; KLIP: Kikuchi-like inflammatory pattern; R-IPSS: Revised International Prognostic Scoring System; SLEDAI-2K: systemic lupus erythematosus disease activity index 2000.

Patient Sex Age decade (years)	Treatment / Number of treatment cycles	Hematologic features at treatment begin	Hematologic response	Lupus response
1 **Male** **35-45**	Allo-HSCT	MDS-IB2 Marrow blasts: 15% Karyotype: normal NGS: *TP53* 48%	Complete response	Complete remission
2 **Male** **75-85**	AZA + Venetoclax: 6 cycles	AML Marrow blasts 29% Karyotype: normal NGS: *IDH2* 37%, *SRSF2* 32%, *CEBPA* 5%	Complete response	Complete remission
3 **Female** **70-80**	AZA: 33 cycles	MDS-IB1 Low transfusion dependence / Neutropenia / Thrombocytopenia Marrow blasts: 6% Karyotype: del 5q NGS: *TET2* 71% *ASXL1* 6%	Partial response *	Complete remission
4 **Male** **55-65**	AZA: 16 cycles	MDS with multiple lineage dysplasia and high transfusion dependance and then progression to CMML-1 Marrow blasts: 7% Karyotype: normal NGS: *CBL* 15%, *NRAS* 39%, *TET2* 80%, *ZRSR2* 82%.	Progression	No response
5 **Female** **60-70**	AZA: 20 cycles	CMML-1 Marrow blasts: 8% Karyotype: normal NGS: *KRAS* 45%, *ASXL1* 40%.	Stagnation	Clinical response
6 **Female** **65-75**	AZA: 3 cycles	CMML-2 Marrow blasts: 10% Karyotype: normal NGS: *ASXL1* 23%, *CBL* 33%, *TET2* 75%, *KRAS* 26% and *TP53* 2%	Progression	No response
7 **Male** **65-75**	AZA*²: 8 cycles	MDS with multiple lineage dysplasia, anemia without transfusion dependence Marrow blasts: 2% Karyotype: del20q NGS: Normal	Partial response *	Complete remission

Table 2. Hematologic and lupus responses to hematologic therapy in patients with MDS/CMML-associated LE.

Hematologic responses were categorized according to IWG 2018 and 2023 criteria and categorized as: complete response, partial response, progression, or stagnation. Lupus responses are defined as complete remission, clinical response, or no response. All patients presented with lupus activity at the beginning of treatment.

Footnote: * Partial response for patient 3 = (marrow response=optimal, neutrophil response=yes, platelet response=no, erythroid response: yes); Partial response for patient 7 = (erythroid response=yes), *²: only treated for cutaneous manifestations of lupus

Abbreviations: Allo-HSCT: allogeneic hematopoietic stem cell transplantation; AML: acute myeloid leukemia; AZA: azacitidine; CMML: chronic myelomonocytic leukemia; MDS: myelodysplastic syndromes; MDS-IB2: myelodysplastic syndromes with increased blasts 2; MDS-IB1: myelodysplastic syndromes with increased blasts 1.