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Lupuslike Manifestations in Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia

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IMPORTANCE Immune-mediated inflammatory diseases are rare but increasingly reported among patients with myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML). Systemic lupus erythematosus (LE) and cutaneous LE 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 LE associated with MDS/CMML and to compare them with idiopathic LE.

DESIGN, SETTING, AND PARTICIPANTS This retrospective case-control study included nationwide, multicenter data from January 1975 to January 2023. Patients with MDS/CMML who either fulfilled classification criteria for systemic LE or had skin lesions diagnosed as cutaneous LE were included. For MDS/CMML systemic LE, a 2:1 case-control study was conducted with idiopathic systemic LE. Clinical features, centralized skin histopathology, and targeted next-generation sequencing were analyzed. Data were analyzed from May 2022 to June 2025.

MAIN OUTCOMES AND MEASURES The clinical, pathological, and molecular features of LE occurring in the setting of MDS or CMML compared with idiopathic LE.

RESULTS Of 24 included patients, 9 (38%) were female, 15 (63%) were male, and the median (range) age at diagnosis was 65 (32-85) years. A total of 19 were diagnosed with systemic LE and 5 with cutaneous LE. The median (range) follow-up was 4.5 (1-31) years. Cutaneous involvement was the most common manifestation of LE (17 [71%]). Chilblain lupus was the predominant subtype (6 [35%]). Compared with idiopathic systemic LE, patients with MDS/CMML–associated LE were older (median [range] age, 65 [32-85] years vs 23 [11-55] years; $P < .001$), more frequently male (10 [53%] vs 3 [8%]; $P = .008$), had less kidney involvement (2 [10%] vs 27 [71%]; $P < .001$), had less articular involvement (7 [36%] vs 37 [97%]; $P < .001$), and had reduced anti–double-stranded DNA positivity (6 [32%] vs 29 [76%]; $P = .001$). The underlying hematologic diseases included MDS (16 [66%]) and CMML (8 [34%]), with 22 (92%) classified as lower risk (Revised International Prognostic Scoring System score of 3.5 or less). Centralized histopathological review reclassified 6 skin biopsies (50%) as MDS/CMML cutis. Identical myeloid variants were detected in blood and skin in 6 of 8 patients, supporting a clonal inflammatory process. Standard LE therapies were often poorly effective, while clone-directed therapies (azacitidine or allogeneic hematopoietic stem cell transplant) led to parallel hematologic and LE responses in 5 of 7 patients.

CONCLUSIONS AND RELEVANCE In this study, MDS/CMML–associated lupuslike manifestations were a distinct entity mimicking systemic LE or cutaneous LE and characterized by clonal inflammation rather than classic autoimmunity in most cases. Early recognition is important, as treatment may require clone-targeting therapies rather than conventional LE therapy.

Supplemental content

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Myelodysplastic syndromes (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 classic MDS and accompanied by sustained peripheral blood monocytosis.[1] Immune-mediated inflammatory diseases (IMIDs) are observed in 10% to 25% of cases,[2,3] most frequently in patients categorized as low risk according to the International Prognostic Scoring System (IPSS).[4]

In contrast to idiopathic forms, IMIDs associated with MDS/CMML often exhibit atypical features, including 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 one-half of patients.[5]

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.[4] Some studies have suggested a shared genetic susceptibility involving somatic variants in myeloid and lymphoid progenitors, which may underlie both IMIDs and hematologic disorders.[6]

Our group and other specialists in the field have identified a clonal relationship between MDS/CMML and IMIDs, particularly in the skin,[7-9] 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 (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome,[10] where identical somatic *UBA1* variants were found in both hematopoietic cells and skin lesions.[10]

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

Some cases of MDS/CMML–associated LE have been reported, highlighting the advanced age of patients and the refractory nature of the disease.[14] However, to our knowledge, no study has specifically characterized their clinical and immunological spectrum, nor treatment options. Similar to other IMIDs, MDS-associated 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 to comprehensively characterize the clinical, immunological, pathological, and molecular features of LE (either systemic or cutaneous LE) occurring in the setting of MDS or CMML; to compare them with idiopathic systemic LE; and to evaluate treatment responses.

Key Points

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

Findings In this cohort study of 24 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 lupuslike manifestations were a distinct syndrome driven by clonal hematopoiesis, warranting early hematologic evaluation and consideration of clone-directed therapy.

Methods

Study Design

This retrospective, nationwide multicenter study was conducted across 13 tertiary care hospitals and included patients diagnosed with either cutaneous LE or systemic LE associated with MDS or CMML between January 1975 and January 2023. Cases were identified through a call for cases within the Medicine Interne, Hematologie et Oncologie (MINHEMON) group, the Etude des Maladies Systémiques en Dermatologie (EMSED) group, and the Société Nationale Française de Médecine Interne (SNFMI) group. The study complied with Good Clinical Practice and the Declaration of Helsinki and received approval from the Cochin Hospital Institutional Review Board with an exemption for informed consent. Data were collected retrospectively with a standardized case report form, in adherence to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Patients were included if they had a diagnosis of MDS or CMML according to the 2022 World Health Organization criteria[15] as well as a diagnosis of systemic LE fulfilling Systemic Lupus International Collaborating Clinics (SLICC) criteria,[16] or a diagnosis of cutaneous LE 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), or drug-induced lupus or if there was an interval of more than 10 years between the diagnoses of MDS/CMML and LE.

A nonmatched control group of 2:1 with idiopathic systemic LE (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 patients with MDS/CMML–associated systemic LE 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 2 groups rather than compare 2 artificially aligned populations (eFigure 1 in Supplement 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. Cutaneous LE subtypes were classified based on Gilliam and Sontheimer classification.[17] For MDS/CMML, the Revised International Prognostic Scoring System (IPSS-R) was used to stratify patients into lower-risk and higher-risk groups, with a cutoff of 3.5 points for IPSS-R.[21]

Histopathological Review

A centralized review of skin biopsies was conducted by 3 pathologists (M.B., P.R., and P.M.) specialized in cutaneous manifestations of MDS/CMML[8,22,23] and cutaneous LE. Biopsies were classified in cutaneous LE, MDS cutis,[8,9] Kikuchilike inflammatory pattern (KLIP) in cutaneous LE,[24] and plasmacytoid dendritic cell (pDC) dermatosis,[25] taking into account the composition of the infiltrate, the cytological appearance, and the immunophenotype of cells. Distinctions were made between mature pDC CD123$^+$, *TCF4*-positive, myeloperoxidase (MPO)-negative disease found within the dermal lymphocytic infiltrate in cutaneous LE and plasmacytoid dendritic cell dermatoses; histiocytes CD123$^+$, MPO-positive, *TCF4*-negative disease found in KLIP mixed with nuclear debris; and immature atypical myeloid cell CD68$^+$, CD163$^+$, MPO-positive infiltrates found in MDS cutis that can also express few CD123 and TCF4 cells.[21,26,27] 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) 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 common variants in myeloid malignant neoplasms were identified, allowing identification of clinically relevant genetic alterations (eTable 1 in Supplement 1).

Outcome Definitions

LE response was categorized as (1) complete response (CR), defined as disappearance of clinical and biological manifestations (SLEDAI-2K score of 0)[29]; (2) clinical response, defined as resolution of clinical manifestations (clinical SLEDAI-2K score of 0 and persistent biological activity: decreased C3 levels and/or positive anti-double-stranded DNA antibodies); or (3) no response.

Hematological responses were evaluated in accordance with the International Working Group (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 counts and percentages for categorical variables and medians and ranges for quantitative variables. Conventional Fisher exact or χ^2 tests were used as appropriate to compare categorical variables, and the Mann-Whitney *U* test was used to compare continuous variables. Statistical significance was set as $P < .05$, and all *P* values were 2-tailed. Statistical analyses were performed using JMP version 17 (JMP Statistical Discovery). Figures and graphs were created using GraphPad Prism version 8 (GraphPad) and BioRender (BioRender.com). Data were analyzed from May 2022 to June 2025.

Results

Patient Clinical and Immunological Features

Patient characteristics are presented in **Table 1**. Of 24 included patients, 9 (38%) were female, 15 (63%) were male, and the median (range) age at diagnosis was 65 (32-85) years. A total of 19 were diagnosed with systemic LE and 5 with cutaneous LE. LE was diagnosed before MDS in 10 patients (42%), concomitantly (defined as less than 3 months between 2 diagnosis) in 10 patients (42%), and after MDS diagnosis in 4 patients (17%).

Cutaneous involvement was the most common manifestation of LE, affecting 17 patients (71%). Chilblain cutaneous LE was the predominant subtype (6 [35%]), typically localized to the fingers and ears (3 of 6 patients), followed by discoid cutaneous LE (5 [29%]), subacute cutaneous LE (5 [29%]), acute cutaneous LE (4 [24%]), and tumid cutaneous LE (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 patients and pericarditis in 2 patients. Kidney involvement was rare, with 2 patients with lupus nephritis (class III and IV). The median (range) SLEDAI-2K score at diagnosis was 9 (5-16). One patient presented with antiphospholipid syndrome and arterial thrombosis, and another presented with autoimmune hemolytic anemia. The median (range) mean corpuscular volume at LE diagnoses was 94 (72-105) fL.

Antinuclear antibodies were positive in 20 patients (83%), including all patients with systemic LE, with a median (range) titer of 1:160 (1:160-1:1280). Four patients had no antibodies (cutaneous LE). Anti-double-stranded DNA 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-β-2 glycoprotein 1 (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 (hemoglobin less than 10 g/dL [to convert to grams per liter, multiply by 10]) was observed in 11 patients (46%), with a median (range) mean corpuscular volume of 92.5 (72-103) fL; neutropenia (absolute neutrophil count less than 1000 cells/μL [to convert to $\times 10^9$/L, multiply by 0.001]) in 8 patients (33%), and thrombocytopenia (platelets less than 100 cells $\times 10^3$/μL [to convert to $\times 10^9$/L, multiply by 1]) in 7 patients (24%). The median (range)

Table 1. Characteristics of Patients With Myelodysplastic Syndromes (MDS)/Chronic Myelomonocytic Leukemia (CMML)–Associated Lupus Erythematosus (LE)

Characteristic	Patients, No. (%)
Total, No.	24
Demographic characteristics	
Sex	
Female	11 (46)
Male	13 (54)
Age at LE onset, median (range), y	66.5 (32-85)
Lupus features	
Cutaneous involvement	17 (71)
Specific LE features	15 (63)
Chilblain cutaneous LE	6 (25)
Discoid cutaneous LE	5 (21)
Subacute cutaneous LE	5 (21)
Acute cutaneous LE	4 (17)
Tumid cutaneous LE	4 (17)
KLIP	2 (8)
Articular involvement	9 (38)
Serositis	7 (29)
Kidney involvement	2 (9)
Autoantibodies	
ANA	
ANA positivity	20 (83)
Titer, median (range)	1:160 (1:160-1:1280)
Anti-double-stranded DNA positivity	6 (25)
Anti-SSA	3 (13)
Anti-SSB	2 (8)
Antinucleosome	3 (13)
Anti-RNP	2 (8)
Anti-Sm	2 (8)
Anticardiolipin	2 (8)
Anti-B2GP1	3 (13)
Lupus anticoagulant	1 (4)
Decreased C3 levels	10 (43)
Decreased C4 levels	9 (38)
Hemolytic autoimmune anemia	1 (4)
Antiphospholipid syndrome	1 (4)
SLEDAI-2K at LE diagnosis, median (range)	9 (5-16)
Hematological features at MDS/CMML onset	
Hemoglobin, median (range), g/dL	1.08 (0.52-1.43)
Platelets, median (range), $\times 10^3$/μL	130 (31-457)
Neutrophil count, median (range), cells/μL	1215 (60-12000)
Monocytes in 8 patients with CMML, median (range), cells/μL	1950 (1600-2500)
Dysgranulopoiesis	13 (54)
Dyserythropoiesis	9 (38)
Dysmegakaryopoiesis	12 (50)
Bone marrow blasts, median (range), %	3 (0-18)
Abnormal marrow cytogenetics	
Del20q	6 (25)
Other	3 (13)
World Health Organization 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 stage	8 (33)
CMML-0	5 (22)
CMML-1	2 (9)
CMML-2	1 (4)
Lower-risk MDS/CMML (IPSS-R score ≤3.5)	22 (92)

Abbreviations: ANA, antinuclear antibodies; APS, antiphospholipid syndrome; B2GP1, β-2 glycoprotein 1; IPSS-R, Revised International Prognostic Scoring System; KLIP, Kikuchilike inflammatory pattern; MDS-LB, myelodysplastic syndrome with low blasts; RNP, ribonucleoprotein; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

SI conversion factors: To convert hemoglobin to g/L, multiply by 10; neutrophil count to $\times 10^9$/L, multiply by 0.001; platelets to $\times 10^9$/L, multiply by 1; monocytes to $\times 10^9$/L, multiply by 0.001.

monocyte count in patients with CMML was 1950 (1600-2500) cells/μL (to convert to $\times 10^9$/L, multiply by 0.001). Bone marrow blasts of 5% or greater were observed in 4 patients (median [range] blasts, 6.5% [6%-18%]).

Cytogenetic analysis was available for 22 patients (92%). A normal karyotype was observed in 13 patients (59%). Abnormalities included del20q (n = 6), del5q (n = 1), and del11q (n = 1) and 1 patient with both del(11q) and del(9q). NGS was performed in 19 patients (79%), using targeted myeloid panels. The most frequently variant genes were *TET2* (8 [42%]), *KRAS* (7 [37%]), *ASXL1* (5 [26%]), *SRSF2* (4 [21%]), and *CBL* (3 [16%]). *TET2*, *SRSF2*, *CBL*, and *TP53* were the most common variants in patients with MDS, whereas *KRAS*, *ASXL1*, and *TET2* predominated in CMML. Details are presented in eFigure 2 in Supplement 1. Tests for *UBA1* variants were negative in 16 of 24 patients and was not tested in 8, as VEXAS syndrome was not suspected (young women without inflammatory syndrome).

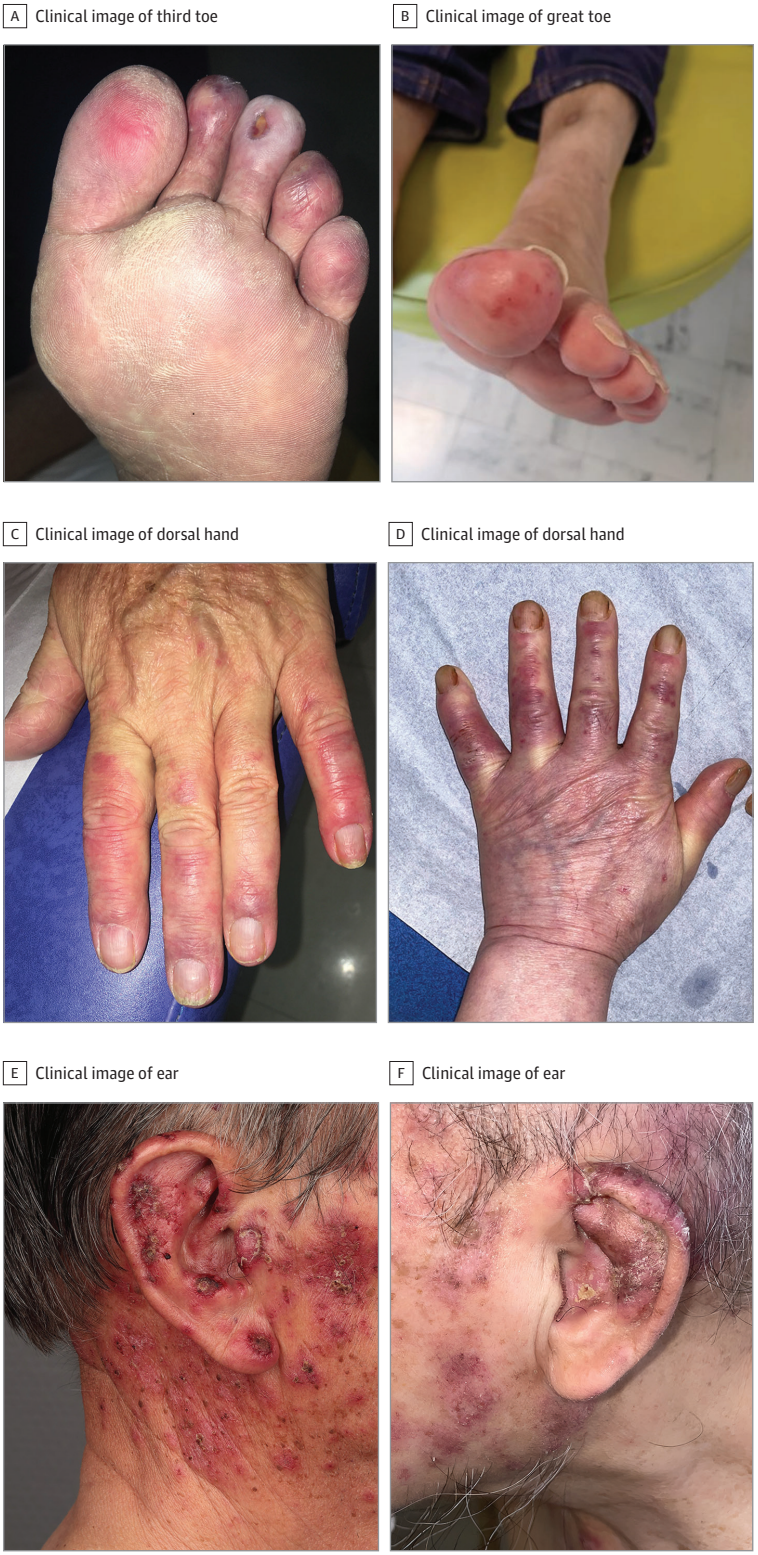
Most patients (22 [92%]) had low-risk MDS/CMML, as defined by an IPSS-R score of 3.5 or less.

Skin Biopsy Findings in Patients With MDS/CMML–Associated LE

A total of 22 skin biopsies of LE lesions taken from 12 patients (71%) were available for centralized review. Detailed results are presented in eTable 2 in Supplement 1.

Histopathological features included dense dermal lymphocytic infiltrates with perivascular and perieccrine involvement in all cases (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 result.

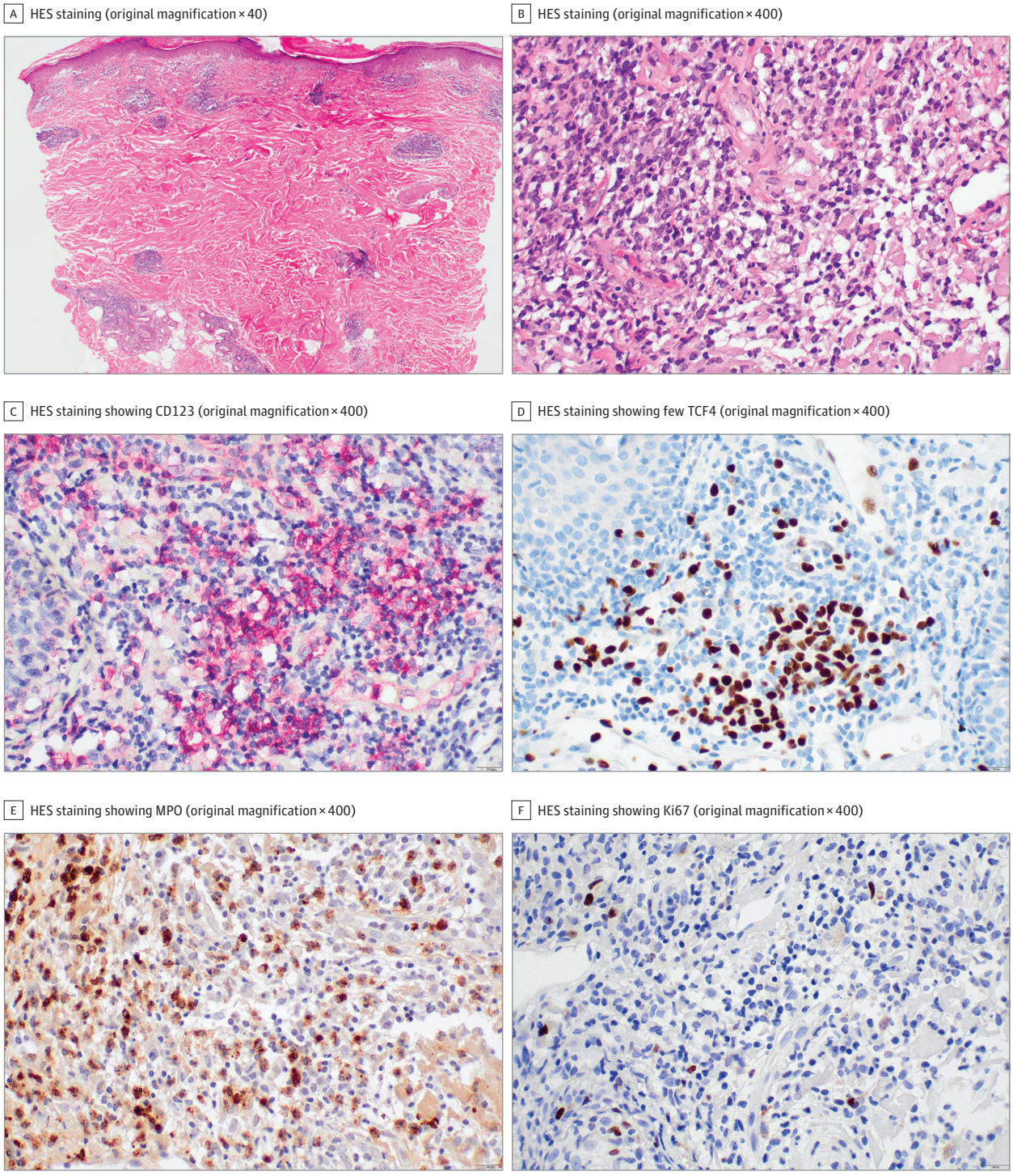
Figure 1. Cutaneous Lesions in Myelodysplastic Syndromes/Chronic Myelomonocytic Leukemia–Associated Lupus Erythematosus



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

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, nonblastic myeloid cells expressing CD68 and MPO with reniform irregular and hyper-

Figure 2. Histopathological and Immunohistochemical Findings in a Patient With Myelodysplastic Syndrome Cutis



A and B, Hematoxylin-eosin-saffron (HES) staining of the skin biopsy revealed a dermal inflammatory infiltrate with dense lymphocyte infiltrate, including perivascular infiltrate and perieccrine infiltrate, with immature precursors; atypical mononuclear cells are observed with reniform irregular and hyperchromatic nuclei. C to F, Immunohistochemical analysis revealed that these atypical cells expressed CD123, few *TCF4*-positive cells, and/or myeloperoxidase-positive cells, with a low Ki67, which supports the diagnosis of MDS cutis.

chromatic nuclei. These clusters were sometimes accompanied by mature neutrophils and often by leukocytoclasia. Ki67 was low (less than 10%).

Four patients (30%) showed cutaneous LE with clusters of histiocytes with a mature pDC phenotype (CD123$^+$, *TCF4*-positive, MPO-negative disease). Only 1 (8%) had the KLIP

phenotype: histiocytes CD163$^+$, CD123$^+$, MPO-positive, *TCF4*-negative mixed with nuclear debris. One patient (8%) showed an appearance of pDC dermatosis with predominant CD123$^+$, *TCF4*-positive, MPO-negative cells.

A targeted myeloid panel NGS was performed on skin biopsy samples from 8 patients with MDS, including 1 who later progressed to CMML-1, although the biopsy was performed at the MDS stage. Identical myeloid variants were detected in the peripheral blood and skin samples of 6 of 8 patients (eTable 2 in Supplement 1). Four of these patients had pathological lesions reclassified as MDS cutis. One patient reclassified as having pDC dermatosis shared a clonal variant in both tissues. Similarly, 1 patient who was reclassified as having a chilblain lupus lesion with shared clonal variants in both tissues, albeit with a low variant allele frequency in the skin sample. In contrast, no variants were detected in the skin biopsy from the KLIP case (eTable 2 in Supplement 1).

Comparison Between MDS/CMML–Associated Systemic LE and Idiopathic Systemic LE

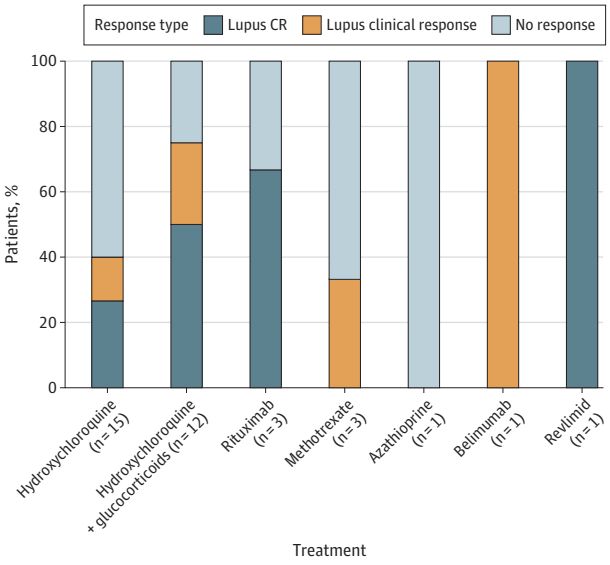
We carried out a case-control analysis comparing the 19 patients with MDS/CMML-associated systemic LE according to SLICC criteria and 38 patients with idiopathic systemic LE. In univariate analysis, patients with MDS/CMML-associated systemic LE were significantly older (median [range] age, 65 [32-85] years vs 23 [11-55] years; $P < .001$), more frequently male (10 [53%] vs 3 [8%]; $P = .008$), had less kidney involvement (2 [10%] vs 27 [71%]; $P < .001$), and had less articular involvement (7 [36%] vs 37 [97%]; $P < .001$) than those with idiopathic systemic LE. This group also showed lower antinuclear antibodies titers (median [range] titer, 1:320 [1:160-1:1280] vs 1:1280 [1:160-1:1280]; $P < .001$), reduced anti-double-stranded DNA positivity (6 [32%] vs 29 [76%]; $P = .001$), and less frequently decreased C4 levels (8 [42%] vs 29 [76%]; $P = .008$) (eTable 3 in Supplement 1).

Treatment and Outcomes

The median (range) follow-up period was 4.5 (1-31) years, during which 7 patients (30%) died: 2 from sepsis (1 while receiving azacitidine treatment), 2 from hematological complications (AML transformation with leucostasis and CMML-2 evolution), 1 from central nervous system bleeding (severe thrombocytopenia), 1 from cardiac failure, and 1 from an unknown cause.

For LE treatment, 15 patients (63%) received hydroxychloroquine alone, at a dose of 5 to 6 mg/kg per day. Among them, 4 patients (27%) achieved CR, 2 (13%) achieved a clinical response, and 9 (60%) showed no response. Twelve patients (50%) received hydroxychloroquine in combination with oral corticosteroids (median [range] dose, 1 [0.4-1] mg/kg per 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 1 showed no response (33%). Other treatments included methotrexate (n = 3), azathioprine (n = 1), belimumab (n = 1), all without CR. One patient with a del20q karyotype had a CR with lenalidomide. All systemic treatment responses are detailed in **Figure 3**. Regarding topical treatments, corticosteroids were used by 13 patients, resulting in a cutaneous LE response in 2 cases (15%). Five patients received topical tacrolimus, but there was no response.

Figure 3. Efficacy of Lupus Therapies in Myelodysplastic Syndromes/Chronic Myelomonocytic Leukemia–Associated Lupus Erythematosus



Bar plot showing lupus erythematosus responses by treatment strategy. Outcomes are categorized as complete response (CR), clinical response, or no response.

Overall, 2 patients progressed to AML: 1 to MDS with increased blasts 2 (MDS-IB2) and 1 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 cutaneous LE and achieved lupus CR following azacitidine treatment (eFigure 3 in Supplement 1). One patient underwent allogeneic stem cell transplant, with hematological CR and lupus CR. This patient had no cutaneous manifestations and has not developed any features of graft vs host disease to date. One patient was treated with azacytidine and venetoclax, resulting in a cytologic CR and lupus CR. Of the 5 patients who received azacytidine, 2 achieved LE CR, with a partial hematological response, 1 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 lupuslike disease. Compared with patients with idiopathic systemic LE, those with MDS/CMML LE were older and predominantly male, exhibiting a distinct clinical and immunological profile. Cutaneous LE involvement was characterized by a

Table 2. Hematologic and Lupus Responses to Hematologic Therapy in Patients With Myelodysplastic Syndromes (MDS)/Chronic Myelomonocytic Leukemia (CMML)–Associated Lupus Erythematosus

Patient No.; sex; age decade, y	Treatment; No. of treatment cycles	Hematologic features at treatment start	Hematologic response[a]	Lupus response[a]
1; M; 35-45	Allogeneic HSCT	• MDS-IB2 • Marrow blasts: 15% • Karyotype: normal • NGS: *TP53*, 48%	Complete response	Complete remission
2; M; 75-85	Azacitidine plus venetoclax; 6 cycles	• AML • Marrow blasts: 29% • Karyotype: normal • NGS: *IDH2*, 37%; *SRSF2*, 32%; *CEBPA*, 5%	Complete response	Complete remission
3; F; 70-80	Azacitidine; 33 cycles	• MDS-IB1 • Low transfusion dependence, neutropenia, and thrombocytopenia • Marrow blasts: 6% • Karyotype: del5q • NGS: *TET2*, 71%; *ASXL1*, 6%	Partial response[b]	Complete remission
4; M; 55-65	Azacitidine; 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; F; 60-70	Azacitidine; 20 cycles	• CMML-1 • Marrow blasts: 8% • Karyotype: normal • NGS: *KRAS*, 45%; *ASXL1*, 40%	Stagnation	Clinical response
6; F; 65-75	Azacitidine; 3 cycles	• CMML-2 • Marrow blasts: 10% • Karyotype: normal • NGS: *ASXL1*, 23%; *CBL*, 33%; *TET2*, 75%; *KRAS*, 26%; *TP53*, 2%	Progression	No response
7; M; 65-75	Azacitidine; 8 cycles[c]	• MDS with multiple-lineage dysplasia, anemia without transfusion dependence • Marrow blasts: 2% • Karyotype: del20q • NGS: normal findings	Partial response[d]	Complete remission

Abbreviations: AML, acute myeloid leukemia; F, female; HSCT, hematopoietic stem cell transplant; M, male; MDS-IB1, myelodysplastic syndromes with increased blasts 1; MDS-IB2, myelodysplastic syndromes with increased blasts 2; NGS, next-generation sequencing.

[a] Hematologic responses were categorized according to International Working Group 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.

[b] Partial response due to an optimal marrow response, a neutrophil response, no platelet response, and an erythroid response.

[c] Only treated for cutaneous manifestations of lupus.

[d] Partial response due to an erythroid response.

high prevalence of chilblain lupus, while kidney 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.[2,3,32]

A key finding of this study is the demonstration that LE-like manifestations in MDS/CMML may be caused by clonal infiltration rather than classic autoimmunity. While MDS/CMML-associated LE frequently exhibits classic histological features of cutaneous LE, our centralized pathological review led to the reclassification of 6 of 12 patients as having MDS/CMML cutis, due to presence of nonblastic dysplastic immature myeloid cells. In 4 cases presenting with MDS cutis, 1 with pDC dermatosis and 1 with chilblain lupus, the same myeloid variants identified in peripheral blood were also present in the skin (eTable 2 in Supplement 1). 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.[8-10]

These findings may have important therapeutic implications. Classic LE therapies (hydroxychloroquine and corticosteroid) were only partially effective, whereas hematologic therapies targeting the clonal disease led to clinical improvement. Among 6 patients receiving azacitidine, 3 achieved a lupus CR and 1 achieved a clinical response. Another patient treated with allogeneic hematopoietic stem cell transplant achieved CR of both LE and hematologic disease.

Interestingly, most patients had low-risk MDS 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.[33-35]

Limitations

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 variants, 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.

Conclusions

In conclusion, MDS/CMML-associated LE represents a distinct inflammatory syndrome, likely mediated by clonal hematopoietic cells rather than classic 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 cutaneous LE, or those with cytopenia or monocytosis—a myeloid neoplasm should be systematically considered. Conversely, the presence of LE-like features in patients with MDS/CMML 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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