

# Acute progression of the leukemic phase in mycosis fungoides and Sézary syndrome



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**Key words:** clinical cases; CTCL classifications; leukemic progression; lymphoma; medical dermatology; mycosis fungoides; Sézary syndrome; T cell.

## INTRODUCTION

Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of skin neoplasms that vary in presentation, histology, and prognosis. The most common subtype is mycosis fungoides (MF), which can range in presentation from patch or plaque stage to tumor stage.<sup>1</sup> Early-stage MF typically entails limited patch or plaque disease, without any nodal or extracutaneous involvement. Usually, it follows an indolent course, with normal life expectancy, although progression of disease and death can occur in a subset of patients.<sup>2,3</sup> On the other hand, Sézary syndrome (SS) is an aggressive form of CTCL, characterized by erythroderma, generalized lymphadenopathy, and clonal atypical lymphocytes in the blood that typically match the clone found in the skin. Patients with advanced subtypes of SS usually have poor overall survival of 2-4 years.<sup>2,4</sup> Presently, the only well-established prognostic marker of the disease is the stage at the time of diagnosis, with better outcomes in those diagnosed with early-stage disease.<sup>1,5</sup>

Although SS is characterized by a blood tumor burden, white blood cell (WBC) counts can be within the normal range or slightly elevated.<sup>1,6</sup> Although a few studies have examined the risk associated with elevated WBC counts at the time of diagnosis, there have not been documented cases of acute, severe leukocytosis during the course of disease.<sup>4,7,8</sup> The recognition of variations in clinical course among patients with MF or SS is important for prompting timely restaging and modification of

### Abbreviations used:

CTCL:	cutaneous T-cell lymphoma
LDH:	lactate dehydrogenase
MF:	mycosis fungoides
SS:	Sézary syndrome
WBC:	white blood cell

overall clinical management in order to improve progression-free survival. Here, we report a case series of 4 patients with MF or SS who experienced clinical deterioration and were found to have acute severe leukocytosis and elevated lactate dehydrogenase (LDH) levels, marking progression of the leukemic phase of CTCL.

## METHODS

We conducted a retrospective review of 4 patients with histologically-confirmed CTCL (2 MF and 2 SS) with complete staging, and we described the clinical and laboratory features of the acute progression of the leukemic phase. The patients were seen in cutaneous lymphoma clinics at Perelman School of Medicine at the University of Pennsylvania (cases 1-3) and at the University Hospital of Zürich (case 4).

MF and SS diagnoses were determined based on the World Health Organization-European Organization for Research and Treatment of Cancer classification of cutaneous lymphomas,<sup>6</sup> stage was determined based on the TNM systems,<sup>9</sup> and stage progression was determined based on the guidelines of the International Society for Cutaneous Lymphomas, the

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**Table I.** Patient demographic, clinical, and laboratory characteristics

Variable	Case 1	Case 2	Case 3	Case 4
CTCL Type	MF	SS	MF	SS
Stage at the time of dx	IA T1aN0M0B0	IVA1 T4NxM0B2	IVA2 T4N3M0B1	IVA1 T4N0M0B2
Interval from dx to leukocytosis	≤ 10 y	≤ 1 y	≤ 3 mo	≤ 18 mo
Prominent clinical features*	Generalized lymphadenopathy	Subcutaneous nodules	Splenomegaly, worsening generalized lymphadenopathy	Cutaneous tumors, worsening pruritus, and erythroderma
CD4/CD8 ratio*	22	NA	118	287
LCT (CD30 <sup>-</sup> or CD30 <sup>+</sup> )*	No LCT on skin biopsy CD30 NA	No LCT on skin biopsy CD30 NA	CD30 <sup>-</sup> LCT on skin biopsy and blood smear but no LCT on lymph nodes	CD30 <sup>+</sup> LCT on skin biopsy
BM involvement*	Yes	Biopsy NA	Yes	Yes
TCR gene rearrangement*	Matching clone in the skin, blood, and BM	Matching clone in the skin and blood (BM NA)	Matching clone in the skin and blood (BM NA)	Matching clone in the skin and blood (BM NA)
Therapy before progression	PUVA therapy, bexarotene gel, interferon alfa	Topical steroids, NB-UVB therapy, extracorporeal photopheresis, interferon alfa, oral bexarotene	Topical steroids, nitrogen mustard ointment, extracorporeal photopheresis	Topical steroids, extracorporeal photopheresis, oral bexarotene
Therapy after progression	Two cycles of romidepsin (after which the patient elected for hospice care)	Gemcitabine	Hyper-CVAD chemotherapy, alemtuzumab, romidepsin	Alemtuzumab, brentuximab vedotin, doxorubicin
Last follow-up status (No. of months after progression)	Deceased (≤ 6 mo)	Deceased (≤ 3 mo)	Deceased (≤ 6 mo)	Deceased (≤ 18 mo)

The patients were in their 60s and 70s, and the group included both men and women.

BM, Bone marrow; CTCL, cutaneous T-cell lymphoma; CVAD, cyclophosphamide, vincristine, adriamycin (doxorubicin), and dexamethasone; Dx, diagnosis; LCT, large cell transformation; MF, mycosis fungoides; NA, not available; NB-UVB, narrow band ultraviolet B; PUVA, psoralen and ultraviolet A; SS, Sézary syndrome; TCR, T-cell receptor.

\*At the time of leukemic progression.

United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organization for Research and Treatment of Cancer.<sup>10</sup> Sample collection and laboratory studies were conducted according to the Declaration of Helsinki principles. All data were deidentified.

## RESULTS

### Baseline

Two patients had MF, and 2 patients had SS (Table I). At the time of diagnosis, the skin lesions varied from limited patch and plaque lesions in a patient with early-stage MF to generalized erythroderma in the patients with SS. Prior to acute leukemia progression, all 4 patients had normal or mildly elevated WBC

counts and LDH levels. Two cases had mild eosinophilia (>500 cells/ $\mu$ L), and 3 had a low absolute CD8<sup>+</sup> cell counts (<250 cells/ $\mu$ L) at the time of diagnosis (Table II).

### Acute progression of the leukemic phase

During the course of the disease, the patients experienced sudden, marked clinical deterioration (Table I), which prompted further laboratory evaluation (Table II). All the patients experienced a rapid and significant increase in WBC count, which we refer to as acute progression of the leukemic phase. The interval from diagnosis to progression ranged from 1 to 96 months. The peak WBC count ranged from 62,000 to 96,000 cells/ $\mu$ L (Table II). The peak of

**Table II.** Laboratory value changes over the progression of the disease

Variable	Case 1 (MF, stage IA)	Case 2 (SS, stage IVA1)	Case 3 (MF, stage IVA2)	Case 4 (SS, stage IVA1)
Percentage of lymphocytes (cells/ $\mu$ L)*	CD4 <sup>+</sup> CD7 <sup>-</sup> 16 (440) CD4 <sup>+</sup> CD26 <sup>-</sup> 8 (232)	CD4 <sup>+</sup> CD7 <sup>-</sup> 55 (650) CD4 <sup>+</sup> CD26 <sup>-</sup> 45 (528)	CD4 <sup>+</sup> CD7 <sup>-</sup> 35 (295) CD4 <sup>+</sup> CD26 <sup>-</sup> 16 (132)	CD4 <sup>+</sup> CD7 <sup>-</sup> 3 (221) CD4 <sup>+</sup> CD26 <sup>-</sup> 93 (6663)
WBC, cells/ $\mu$ L <sup>†</sup>	6800 $\rightarrow$ 83,500 $\rightarrow$ 39,200	8000 $\rightarrow$ 96,000 $\rightarrow$ 7200	6700 $\rightarrow$ 62,000 $\rightarrow$ 16,900	13,400 $\rightarrow$ 85,610 $\rightarrow$ 5590
Eosinophils, cells/ $\mu$ L (%) <sup>†</sup>	50 (0.8) $\rightarrow$ 1570 (4) $\rightarrow$ 0 (0)	700 (8.2) $\rightarrow$ 340 (1) $\rightarrow$ NA	680 (10.2) $\rightarrow$ 2460 (4) $\rightarrow$ 70 (1)	70 (0.5) $\rightarrow$ 210 (<1) $\rightarrow$ 0 (0)
Absolute CD8 <sup>+</sup> count, cells/ $\mu$ L <sup>†</sup>	697 $\rightarrow$ 312 $\rightarrow$ NA	36 $\rightarrow$ 70 $\rightarrow$ NA	126 $\rightarrow$ 59 $\rightarrow$ NA	202 $\rightarrow$ 144 $\rightarrow$ 9
LDH, U/L <sup>†</sup>	138 $\rightarrow$ 513 $\rightarrow$ 334	440 $\rightarrow$ 7639 $\rightarrow$ 710	434 $\rightarrow$ 5725 $\rightarrow$ 476	607 $\rightarrow$ 1230 $\rightarrow$ 619

LDH, lactate dehydrogenase; MF, mycosis fungoides; NA, not available; SS, Sézary syndrome; WBC, white blood cell.

\*Measure of peripheral blood tumor burden at time of diagnosis.

<sup>†</sup>Laboratory values are presented as follows: values at the time of diagnosis  $\rightarrow$  peak value during progression  $\rightarrow$  values after the initiation of new therapy.

leukocytosis was reached within 4-16 weeks. During this time of acute leukocytosis, all 4 patients had elevated LDH levels, ranging from 513 to 7639 U/L (Table II).

We excluded other T-cell leukemia diagnoses, such as adult T-cell leukemia/lymphoma and pro-T-cell prolymphocytic leukemia. The patients either had negative serology for human T-lymphotropic virus type I or were not from endemic areas, making adult T-cell leukemia/lymphoma less likely. Molecular cytogenetic data were available for cases 1 and 4. Case 1 had a normal karyotype, and case 4 had del(9p) at the 9p21 breakpoint, involving the 9p21 (CDKN2A/B) locus, but did not have t(14;14), inv(14), or TCL1 gene rearrangement. Leukemoid reaction was ruled out because workup results for infectious diseases and other etiologies remained negative.

**Outcome**

After initiation of new treatment (Table I), the WBC count decreased for all 4 patients (Table II), normalizing for cases 2 and 4 but remaining at above-normal values for cases 1 and 3. Although the LDH levels were also trending downward, they remained at elevated (>280 U/L) values for all 4 patients. The patients succumbed to the disease within 3-18 months of the progression (Table I).

**DISCUSSION**

In this case series of 4 patients with MF or SS, we documented progression of the leukemic phase, with remarkably elevated WBC counts, ranging from 62,000 to 96,000 cells/ $\mu$ L, which correlated with clinical deterioration. To our knowledge, such an acute event of leukocytosis has not been previously documented. Because of the heterogeneity of CTCL and limited prognostic markers, it is important to recognize and closely study variations in the progression of these malignancies in order to improve management decisions. In our study, 1 patient with progression of the leukemic phase had stable stage IA MF for 8 years, demonstrating that although early-stage disease generally has a good prognosis, it can deviate from its expected course.

The mechanism of acute progression of the leukemic phase in our patients may be similar to that in patients with chronic myeloid leukemia, where a percentage of patients experience a blast crisis that is associated with leukocytosis, clinical deterioration, and poor survival. The blast crisis is thought to occur due to the accumulation of chromosomal and molecular abnormalities that result in the expansion of increasingly malignant cell clones.<sup>11</sup> In our case series, the patients may have

experienced an evolution to a more aggressive T-cell clone. This evolution could be secondary to the loss or gain of certain chromosomal regions, and/or it may be due to alterations in cytokine expression pathways that enhance malignant T-cell clonal expansion while losing anti-tumor cytotoxic properties. Indeed, the loss of the 9p21 (CDKN2A/B) locus containing tumor suppressor genes, as in case 4, has been known to be associated with shorter survival in patients with CTCL and an aggressive subset of disease.<sup>12,13</sup> Furthermore, prior systemic treatments might also be predisposing factors for acute progression of the leukemic phase.

Studies have found eosinophilia and low CD8<sup>+</sup> cell counts to be markers of poor prognosis in patients with CTCL.<sup>8,14</sup> Two of the patients in our case series had mild eosinophilia at the time of diagnosis, and 3 had low CD8<sup>+</sup> cell counts, which may be associated with progression. A limitation of our study is the small number of cases and the retrospective, observational case series design. Acute progression of the leukemic phase in patients with MF or SS is likely underreported. As more cases are identified based on the awareness raised by this report, further research on prognostic associations and appropriate management can be performed in larger cohorts. Targeted antibodies and immunotherapeutic agents that are now available or in the pipeline have the potential to halt the progression of the disease when initiated in a timely manner in appropriate patients, such as in our cases. These therapeutics include mogamulizumab (anti-CCR4 antibody), which was not yet approved by the US Food and Drug Administration at the time of the diagnosis and treatment of these cases, as well as emerging immune checkpoint inhibitors, chimeric antigen receptor T-cell therapy, and anti-CD47 and anti-KIR3DL2 antibodies.<sup>15</sup>

In summary, our case series informs the necessity of recognizing that acute progression can occur in patients with MF or SS. There should be a low threshold to restage patients with signs of clinical deterioration and abrupt leukocytosis after ruling out infectious and other malignant etiologies. A multidisciplinary team approach with oncologists and dermatologists is crucial to assess tumor burden in different compartments (skin, lymph nodes, blood, bone, and viscera). In addition, prompt modification of the overall clinical management is warranted to improve progression-free survival. As more cases are identified, future research through emerging technologies such as single-cell RNA sequencing can potentially expose the differences in the selection of malignant T-cell subpopulations at the time of progression of the

leukemic phase of CTCL and inform tailored treatment options.

#### Conflicts of interest

Dr Dummer reports intermittent, project-focused consulting and/or advisory relationships with Novartis, Merck Sharp and Dhome, Bristol-Myers Squibb, Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome, Regeneron, and Alligator outside the submitted work. Dr Ramelyte reports intermittent, project-focused consulting and/or advisory relationships with Amgen, Novartis, Sanofi, Pierre Fabre, and Sun Pharma outside the submitted work. Dr Kim reports grants and personal fees from Actelion and Galderma; personal fees from Helsinn and Almirall; and grants from MedImmune, Kyowa Kirin, and Soligenix outside the submitted work. Drs Maredia, Cozzio, and Rozati have no conflicts of interest to declare.

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