Double-Positive $CD4^+CD8^+$ Sézary Syndrome: An Unusual Phenotype With an Aggressive Clinical Course

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Practice Points

- Sézary syndrome is an aggressive form of cutaneous T-cell lymphoproliferative disease associated with severe pertubations in the immune system.
- The skin biopsy is frequently nondiagnostic and diagnosis rests on correlating the clinical presentation of erythroderma with peripheral blood abnormalities, most notably T-cell clonality, circulating T cells showing a loss of CD7, and a high CD4:CD8 ratio.
- Although the dominant phenotype is $CD4^+$, as with conventional mycosis fungoides there is some heterogeneity in the phenotypic profile. A double-positive phenotype could be reflective of an unusually aberrant cytokine milieu; an excessive helper T cell (TH2) imbalance could result in the secondary acquisition of CD8 in a neoplastic $CD4^+$ lymphocyte. A more aggressive clinical course might be expected in such rare cases of double-positive Sézary syndrome.

Sézary syndrome (SS) is a rare aggressive form of cutaneous T-cell lymphoma. When patients die from SS, it frequently is due to the sequela of the profound endogenous immunosuppression that is typical of this condition. Most cases of SS represent neoplasms of mature postthymic $CD4^+$ T cells. We present a case of SS that exhibited an unusual double-positive phenotype in which the neoplastic T cells demonstrated CD4 and CD8 expression. The patient's clinical course was unusually aggressive with rapid clinical demise occurring less than 1 year from the initial cutaneous eruption. Our patient had documented involvement of the skin, peripheral blood, and lymph nodes.

We also review other anecdotal reports of postthymic T-cell lymphomas manifesting as a double-positive phenotype primarily in the context of adult T-cell leukemia and T-cell lymphoma. The evolution of the postthymic double-positive T-cell phenotype, especially with regard to SS, and the benign lymphocyte counterpart also is discussed.

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Sézary syndrome (SS) is an aggressive form of cutaneous T-cell lymphoma characterized by generalized erythroderma and circulating neoplastic T cells that exhibit a distinct cerebriform morphology (ie, Sézary cells) indistinguishable from mycosis fungoides (MF). Lymphadenopathy is common in SS, and patients may develop alopecia, nail

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dystrophy, and eye changes in cases of advanced disease.[1] The 3 main variants of SS are de novo SS, SS arising in a setting of MF, and SS that may develop in a background of idiopathic erythroderma. Idiopathic erythroderma may be difficult to distinguish from primary de novo SS. The main distinction is the lack of sufficient diagnostic peripheral blood criteria to warrant SS categorization.[2-4]

The malignant cells in SS are characterized as atypical skin-homing $CD4^+$/$CD45RO^+$ T cells that lack certain pan T cell markers, including CD7, CD62L, CD5, and CD26. The vast majority of MF and SS cases are of the $CD4^+$ subset; however, other T-cell subsets can be implicated, most notably $CD8^+$ and double-negative variants.[5] Although earlier phases of MF are characterized by a helper T cell (T_H1) cytokine profile, progressive disease in the setting of MF and SS is associated with a T_H2 cytokine profile with increased levels of IL-4, IL-5, IL-7, IL-10, and IL-18.[4] A dysregulated T_H2-dominant profile contributes to the poor prognosis associated with SS and advanced MF.[6] In particular, the chronic local overproduction of IL-4, IL-5, and IL-10 decreases recruitment of reactive $CD8^+$ T cells, thereby allowing tumor cells to evade the host antitumor immune response.

Diminished T_H1 cytokine production in the peripheral blood is associated with a decrease in IL-12 and IFN-γ, which causes a decline in myeloid and plasmacytoid dendritic cells as well as $CD56^+$ natural killer cells,[7] further contributing to deterioration in both immune function against microbial organisms and host antitumor immunity. As a consequence, SS patients have a high incidence of bacterial, herpetic, and secondary malignant processes leading to notable morbidity and mortality.[8-10] Peripheral eosinophilia and high levels of IgE are independent markers for poor prognosis and disease progression and are attributable to the effects of another T_H2 cytokine, namely IL-5.[11] An additional hypothesis explaining immunosuppression in advanced disease comes from in vitro findings indicating that immature dendritic cells can induce Sézary cells to develop regulatory T cell activity with an increased potential to diminish $CD8^+$ T cell effector functions against microbial pathogens and tumor cells.[3,12-15]

We present a case of a novel phenotypic variant of SS, namely one with a double-positive $CD4^+CD8^+$ T cell phenotype. The clinical, histologic, and phenotypic features are discussed in detail, along with a review of the literature describing other forms of postthymic double-positive T-cell lymphoma.

CASE REPORT

A 52-year-old black woman with no relevant medical history presented to our dermatology clinic with a generalized, intensely pruritic eruption that had been progressing for 7 months. She was subsequently referred to a dermatologist who performed a biopsy that was interpreted as a reactive dermatitis with features of eczema. Outside dermatologists previously treated her with 2 short prednisone tapers that did not ameliorate her symptoms.

On physical examination, the patient was erythrodermic with numerous malodorous, scaly, erythematous patches and plaques involving 60% of the body surface area (Figure 1). Alopecia of the scalp and face, nail pitting, maceration of the inguinal folds, and cervical lymphadenopathy also were observed.

Clinical laboratory evaluation showed eosinophilia with an eosinophil count of 500/μL (reference range, 0–300/μL) and a negative antinuclear antibody test. The clinical presentation and histopathologic findings suggested a diagnosis of atopic dermatitis. The patient was treated with cyclosporine. She also was started on oral cephalexin and econazole nitrate cream to reduce bacterial and fungal colonization. Following a 1-month course of cyclosporine, some modest improvement was noted.

A repeat biopsy performed 1 month later was consistent with SS. Comprehensive peripheral blood studies showed a total lymphocyte count of 2761/μL (reference range, 1400–2900/μL) in which 77% of the cells expressed CD2; similar to the skin biopsy, there was coexpression of CD4 and CD8 with a reduction in the expression of CD7. There were more than 1000 Sézary cells per microleter and there was evidence of peripheral blood T-cell clonality. A diagnosis of SS

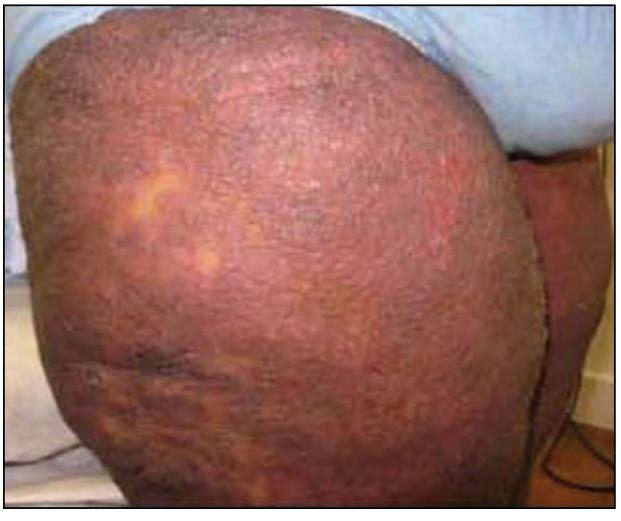

Figure 1. Erythroderma with superimposed psoriasiform plaques and extensive scaling of the skin observed on the right lower leg.

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stage B2b (>1000 Sézary cells per microleter) was rendered. A detailed account of the flow cytometry of the peripheral blood specimen is provided in Table 1. In light of this new diagnosis, cyclosporine was tapered (Table 2).

Following her skin biopsy interpretation of SS along with confirmatory peripheral blood studies, the hematology department was consulted and recommended complete staging with positron emission tomography and computed tomography, which showed numerous hypermetabolic lymph nodes in the bilateral axillary region, chest, and pelvis. Although the patient refused a bone marrow biopsy, she agreed to chemotherapy recommended by the hematology and oncology departments; however, the administration of chemotherapy was delayed, as the patient became febrile. Methicillin-resistant *Staphylococcus aureus* was found in the patient's blood and urine. Her kidney function worsened with a creatinine level rising to 2.6 mg/dL (reference range, 0.6–1.2 mg/dL) from a baseline of 0.9 mg/dL recorded on initial presentation. The renal service was consulted, and subsequent workup suggested acute tubular necrosis secondary to hypotension, which was consistent with systemic inflammatory response syndrome.

The patient experienced a difficult clinical course. Three weeks after the inguinal node biopsy, which was performed 9 weeks after her initial presentation to our dermatology clinic, she began her first course of CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone). Shortly after initiation of chemotherapy she became hypothermic (body temperature, 33°C) with a white blood cell count of 12,900/μL (reference range, 3400–11,200/μL), though all blood cultures were negative.

After completing her first course of chemotherapy, the patient developed several infections, including a multiresistant *Klebsiella pneumoniae* infection of the urinary tract. The patient died 1 year after initial presentation due to multiorgan failure secondary to polymicrobial sepsis.

Pathology

Light Microscopy—A superficial shave biopsy taken from the left antecubital fossa at the time of her initial presentation demonstrated a psoriasiform pattern of epidermal hyperplasia with a diminished granular cell layer and parakeratosis. There was minimal exocytosis of lymphocytes into the epidermis (Figure 2A). Bacterial colonies were present in the stratum corneum. Substantial lymphoid atypia was not observed. The biopsy was interpreted as representing a subacute eczematous dermatitis with secondary impetiginization at a prior dermatology visit and on presentation to our dermatology clinic.

Table 1.

Flow Cytometry[a]

Cell Surface Marker	Positive Cells, %
CD2	77
CD3	89
CD4	82
CD5	89
CD7	33
CD8	46
CD10	<1
CD11b	0
CD13	0
CD14	0
CD15	0
CD16	0
CD19	7
CD20	9
CD22	0
CD23	11
CD33	0
CD34	0
CD38	5
CD52	100
CD56	8
CD57	7
CD117	0
TdT	<1
κ	4
γ	2

Abbreviation: TdT, terminal deoxynucleotidyl transferase.
[a]Selective gating of 83% of cells from peripheral blood.

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After presenting to us, the patient consented to an additional punch biopsy. On deeper biopsy a severely atypical angiocentric lymphocytic infiltrate was identified (Figure 2B) in concert with small foci of epitheliotropism. The lymphocytes ranged from intermediate to large in size with substantial nuclear contour irregularity, including many cells with large cerebriform morphologies. Mitotic activity was readily discernible.

Immunohistochemistry—Phenotypic studies were conducted 1 month after presentation to our dermatology clinic. The lymphocytes were positive for CD2,

Table 2.

Lymphocyte Subset Studies

Lymphocyte Analysis	Reference Range	No. at 7 Months After Initial Presentation (%)	No. at 1 Month[a] After Cyclosporine Therapy (%)
Total lymphocyte count	1514–3266/μL	1369/μL	2761/μL
T lymphocyte CD3	1001–2407/μL	1095/μL (80)	2430/μL (95)
B lymphocyte CD19	56–610/μL	192/μL (14)	221/μL (8)
Helper T cell CD4	588–1202/μL	972/μL (71)	2209/μL (80)
T suppressor CD8	394–672/μL	575/μL (42)	1242/μL (45)
T lymphocyte $CD56^{+}16$	94–484/μL	68/μL (5)	83/μL (3)
CD4:CD8 ratio	1.1–2.3	1.7	1.8
$CD3^{+}CD4^{+}CD8^{+}$	0	465/μL (34)	1077/μL (39)

[a]8 months after initial presentation.

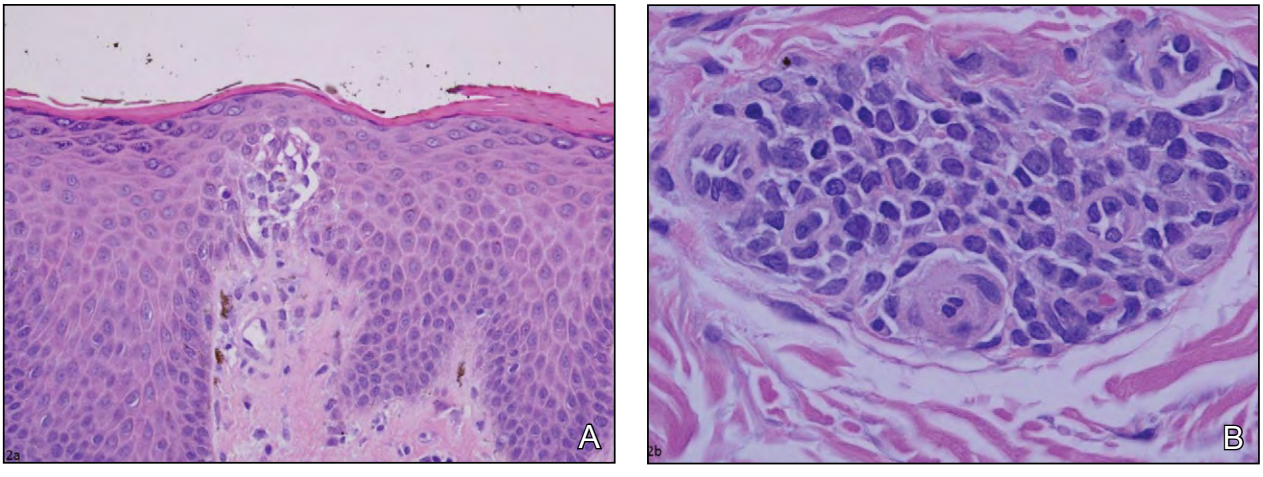

Figure 2. The epidermal changes were not diagnostic of lymphoma but rather showed a morphology more in keeping with a diagnosis of subacute eczematous dermatitis, a diagnosis rendered on prior biopsies. In particular, there was a psoriasiform pattern of epidermal hyperplasia with focal exocytosis of lymphocytes and Langerhans cells into the epidermis, with a Langerhans cell–rich microvesicle (A)(H&E, original magnification ×200). In contrast, the dermal infiltrate showed an angiocentric infiltrate of larger blastic-appearing cells in the 15- to 20-μm size range (B)(H&E, original magnification ×1000). There also were smaller cells with a cerebriform morphology within this perivascular infiltrate.

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CD3, and β-F1, and appeared to express both CD4 and CD8 (Figure 3). Although there was focal preservation of CD62L, there was a complete loss of CD7. There was no staining for granzyme B; CD56; *TCL1* (T-cell leukemia/lymphoma 1) oncogene; forkhead box P3 gene, *FOXP3*; or CD25. Additionally, there were no reactive *FOXP3* cells in the infiltrate. The terminal deoxynucleotidyl transferase was negative. A subsequent lymph node biopsy demonstrated partial effacement by a neoplastic T cell populace, exhibiting a phenotype profile identical to the one found in the skin and peripheral blood samples.

Molecular Studies—Polymerase chain reaction gene rearrangement studies analyzed by polyacrylamide gel electrophoresis revealed identical monoclonal T-cell populations in the skin, peripheral blood, and lymph nodes.

COMMENT

The patient met all of the criteria for diagnosis of SS. Historically, SS manifests with the triad of erythroderma; generalized lymphadenopathy; and the presence of neoplastic T cells in the skin, peripheral blood, and lymph nodes.[2] Our patient also met the hematologic criteria for diagnosis of SS described by the International Society for Cutaneous Lymphomas based on the presence of T-cell clonality, the percentage of circulating $CD7^-$ T cells, and the number of circulating Sézary cells.[16]

The phenotypic profile of the neoplastic cells in our patient comprised $CD2^+CD3^+CD4^+CD8^+$ T cells with a loss of CD7 and terminal deoxynucleotidyl transferase. A double-positive $CD4^+CD8^+$ phenotype is a unique presentation. CD4 and CD8 are key molecules in T cell differentiation and function. In the normal development of T cells, expression of CD4 and CD8 is tightly regulated. Cells destined to become T cells enter the outer cortex of the thymus via the bloodstream. These double-negative $CD4^-CD8^-$ cells rapidly proliferate and undergo simultaneous rearrangement of β, Δ, and γ T-cell receptor (TCR) chains. Pre-TCR signaling components trigger double-negative $CD4^-CD8^-$ cells to become double-positive $CD4^+CD8^+$ thymus-derived T lymphocytes. After positive and negative selection of late-stage thymocytes, they subsequently mature into single-positive $CD4^+$ or $CD8^+$ T cells and migrate to peripheral tissues.

Although double-positive T cells are characteristic of thymic cortical T cells, there now is an emerging body of literature describing double-positive postthymic T cells, which can be found in the peripheral blood of normal, healthy, elderly individuals.[17] Double-positive postthymic T cells also have been found to play effector and immunoregulatory roles in the control of the inflammatory response in the setting of breast cancer, melanoma, cutaneous T-cell lymphoma, nodular lymphocyte-predominant

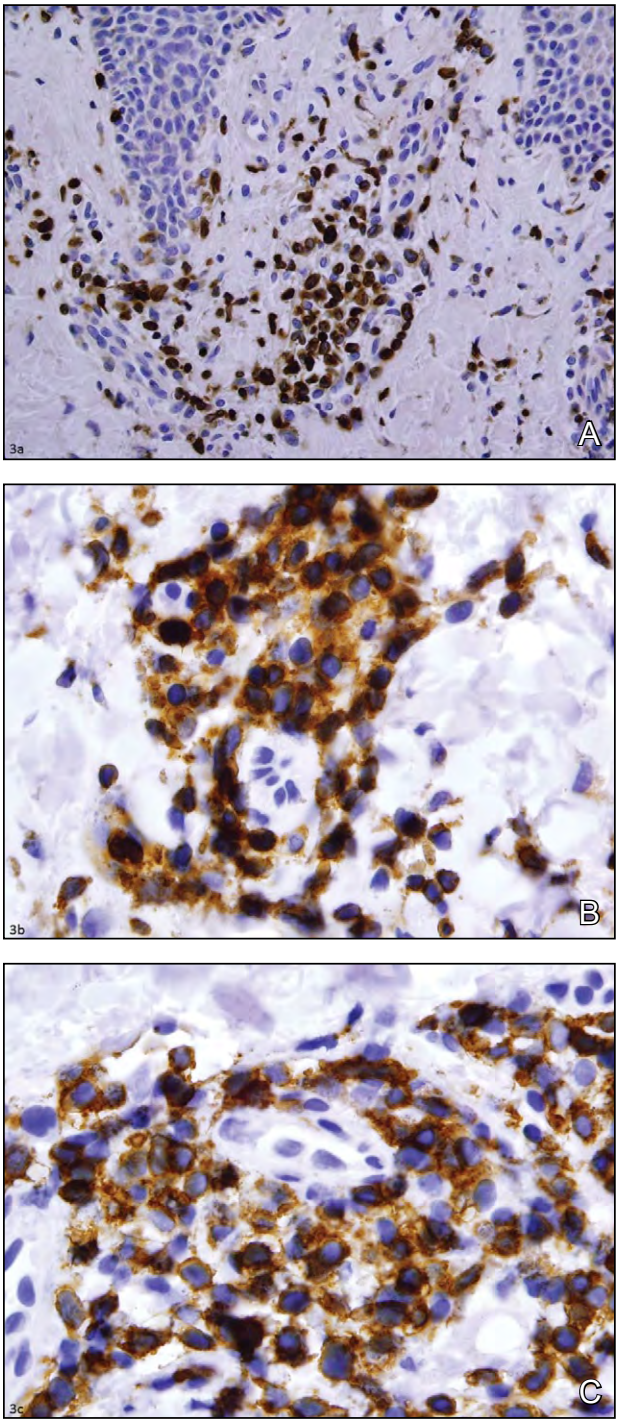

Figure 3. Phenotypic studies demonstrated β-F1 positivity amidst the neoplastic lymphocytes (A)(original magnification ×400); there was positive staining of the neoplastic cells for CD4 (B)(original magnification ×1000) and CD8 (C)(original magnification ×1000).

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Table 3.

Reported Cases of Double-Positive Postthymic T-Cell Malignancies

Reference (Year)	Age, y	Gender	Diagnosis	Distribution	Treatment	Outcome
Tamura et al[26] (1987)	63	F	ATLL	Lymph node, lung	IFN-β, IFN-γ	Progression, death
Murata et al[27] (1992)	47	F	ATLL	Face/trunk	Combination therapy[a]	Regression then death
	63	M	ATLL	Extremities	Combination therapy[a]	Regression then death
	64	F	ATLL	Skin	Combination therapy[a]	Regression then death
	66	M	ATLL	Lymph node	Combination therapy[a]	Regression then death
Mizuki et al[28] (1998)	N/A	N/A	LGLL	N/A	N/A	N/A
	N/A	N/A	LGLL	N/A	N/A	N/A
	N/A	N/A	ATLL	N/A	N/A	N/A
	N/A	N/A	ATLL	N/A	N/A	N/A
	N/A	N/A	ATLL	N/A	N/A	N/A
Ciminale et al[29] (2000)	56	F	ATLL	Lymph node	mBACOD[b]	Death
Kim et al[30] (2006)	67	M	ATLL	Neck, trunk, lymph node, liver	N/A	Death
Current case (2014)	52	F	SS	Generalized erythroderma	Combination therapy[a]	Death

Abbreviations: F, female; ATLL, adult T-cell leukemia lymphoma; M, male; N/A, not available; LGLL, large granular leukemia lymphoma; SS, Sézary syndrome.

[a]CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone).

[b]Methotrexate with leucovorin, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone.

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Hodgkin lymphoma, viral infection, and autoimmune disease.[18-25] The exact function of these cells has yet to be elucidated, but it likely is in the context of immunoregulatory function. Dual CD4/CD8 expression has been described in anecdotal case reports of postthymic T-cell malignancies, primarily in the context of adult T-cell leukemia and large granular lymphocyte leukemia. Table 3 is a summary of select cases of double-positive postthymic T-cell malignancies that have been reported.

There are potential events that could lead to the emergence of a double-positive postthymic T cell. As described by Mizuki et al,[28] the CD8 molecule is composed of α and β subunits. Although double-positive postthymic T cells and peripheral $CD8^+$ single-positive T cells express the αβ subtype (CD8αβ), mature single-positive CD4 cells can become peripherally activated via IL-4 to weakly express an αα subtype (CD8αα). After staining with anti-CD8 immunofluorescence, CD8αα was associated with a dim signal for CD8 cells, while the CD8αβ cells demonstrated a bright pattern of immunofluorescent labeling for CD8.[28] In addition, a single-positive CD8 T cell can be induced to express CD4 after activation with TCR cross-linking; however, one study suggested that double-positive T cells may represent a distinct subset of T cells that express CD4 and CD8 at their inception as opposed to a later-stage event characterized by acquisition of a secondary coreceptor such as CD4 or CD8.[31]

In our patient, flow cytometry revealed that 46% of cells were $CD8^+$, while 82% of cells were $CD4^+$, which indicated that the neoplastic cells likely were originally single-positive $CD4^+$ cells that became peripherally activated to express CD8, likely CD8αα. Our hypothesis lies in accordance with the normal $CD4^+CD8^-$ phenotype of typical Sézary cells. The concomitant expression of CD8, more specifically the α subunit of CD8, may be on the basis of the high levels of IL-4, reflecting the dysregulated T_H2-dominant cytokine milieu intrinsic to SS. In fact, the presence of the double-positive neoplastic T cells may be indicative of a more extreme T_H2 skewing with its associated deleterious effects, especially in regard to endogenous immunosuppression.

CONCLUSION

We report an unusually aggressive variant of double-positive $CD4^+CD8^+$ SS. We postulate that the expression of CD8 was part of an aberrant phenotype potentially induced by a dysregulated T_H2-dominant cytokine milieu. It is quite possible that a correlation may exist between the number of circulating double-positive neoplastic T cells and prognosis. These studies have yet to be conducted.

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