# Rapid progression of immune dysregulation in an HIV-infected patient with Sézary syndrome

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**Abstract** A 44-year-old man known to have human immunodeficiency virus (HIV) infection presented to our clinic with erythroderma, generalized lymphadenopathy, and cutaneous nodules and tumors. After a series of investigations, we confirmed that he had Sézary syndrome. In this paper we describe the immune alterations that occur in both Sézary Syndrome and HIV infection and how these changes together resulted in rapid and overwhelming immune dysregulation in our patient.

*Keywords: cutaneous T-cell lymphoma, Sézary syndrome, immune suppression, HIV/AIDS*

## Introduction

Sézary syndrome can be defined as an erythrodermic cutaneous T-cell lymphoma with leukemic involvement of malignant T-cells [1]. We report a case of an HIV-infected patient with Sézary syndrome, who experienced rapid and overwhelming immune dysregulation.

## Case Synopsis

A 44-year-old man presented to our dermatology clinic in November 2017 with a history of having developed multiple skin lesions over an eight-month period. He was diagnosed with HIV infection in mid-2015 and he was adherent to highly active antiretroviral treatment (HAART) since then. On examination he was found to be erythrodermic and he had multiple cutaneous nodules and tumors, some of which were ulcerated and secondarily infected (**Figure 1**). Palmoplantar keratoderma, onychodystrophy, leonine facies, and loss of eyebrows were noted. Generalized, significant lymphadenopathy was also present. Routine monitoring of the patient's CD4 count and HIV viral load were done at his primary health care facility. There was an increase in CD4 count from 432 cells/µl in January 2017 to 5313 cells/µl in August 2017. During the same period the viral load increased from being undetectable to 8308 copies/ml.

Peripheral blood morphology showed that atypical lymphocytes accounted for approximately 35% of all nucleated white blood cells; cells were small to medium in size with cerebriform nuclei characteristic of Sézary cells (**Figure 2**). Flow cytometry and immunophenotyping on peripheral blood were done. The lymphocyte population of interest had bright CD45 expression and was positive for CD2, CD3, CD4, and CD5, but did not express CD7, CD8, CD19, CD20, or CD25. The absolute Sézary cell count was 9800 cells/µl and the CD4:CD8 ratio was >10. T-cell receptor gene rearrangement studies confirmed a monoclonality on the peripheral blood specimen.

Skin biopsy revealed a dense monomorphic lymphocytic infiltrate dominated by atypical cells in the superficial and deep dermis (**Figure 3A**). The neoplastic infiltrate showed follicular and perifollicular accentuation with follicular infiltration by atypical lymphocytes with a cerebriform appearance. Immunohistochemistry was positive for CD3, CD4, CD5, CD45, and negative for CD8, CD20, and CD30 (**Figure 3B**). T-cell receptor gene rearrangement studies were not performed on skin.

An enlarged cervical lymph node was excised and investigated. Histopathology revealed atypical

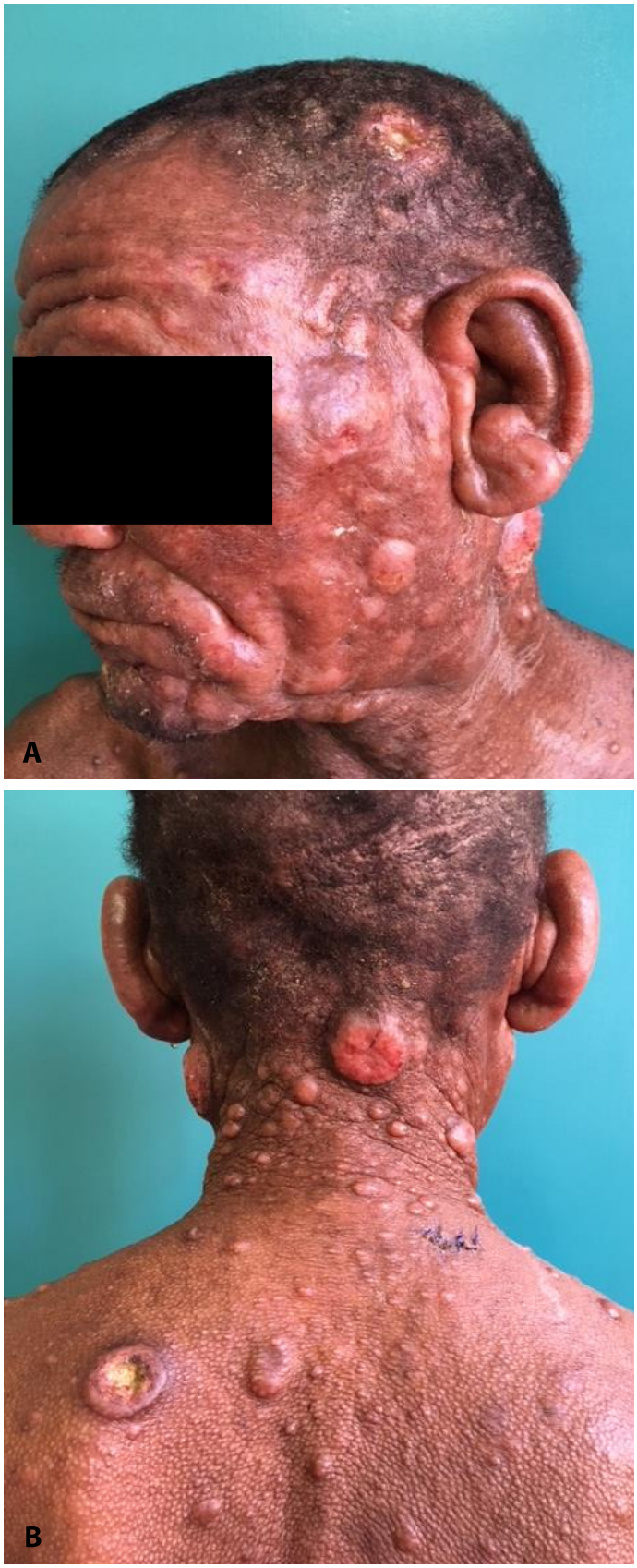


**Figure 1**. *Erythroderma, multiple cutaneous nodules and tumors **(A, B)**, and leonine facies with loss of eyebrows **(A)**.*

reactive change, whereas immunohistochemistry revealed a CD4 pattern of staining that was in keeping with LN3 disease (LN 0-4 NCI Classification System) based on the extent of the atypical T-cell infiltrate within the lymph node. Ultimately, T-cell receptor gene rearrangement studies excluded a significant clonal T-cell proliferation within the lymph node. Computed tomography (CT) revealed axillary and inguinal lymph nodes measuring >2cm. CT also revealed multiple hepatic and splenic hypodensities and multiple pleural-based and parenchymal nodules. Organ involvement was not confirmed histologically.

The patient's initial clinical findings were in keeping with that of Sézary syndrome (SS) or tumor stage mycosis fungoides (MF). After all investigations were completed, we diagnosed the patient with SS according to the WHO and ISCL/EORTC guidelines. He was staged as T4N2MXB2, or stage $IVA_1$, based on the NCCN guidelines. We treated the erythroderma and secondarily infected cutaneous lesions and we continued HAART. The patient was referred to a specialized hematology-oncology unit for urgent evaluation and treatment. However, the patient did not attend subsequent appointments with the hematology-oncology department. After further inquiry, we discovered that the patient had died

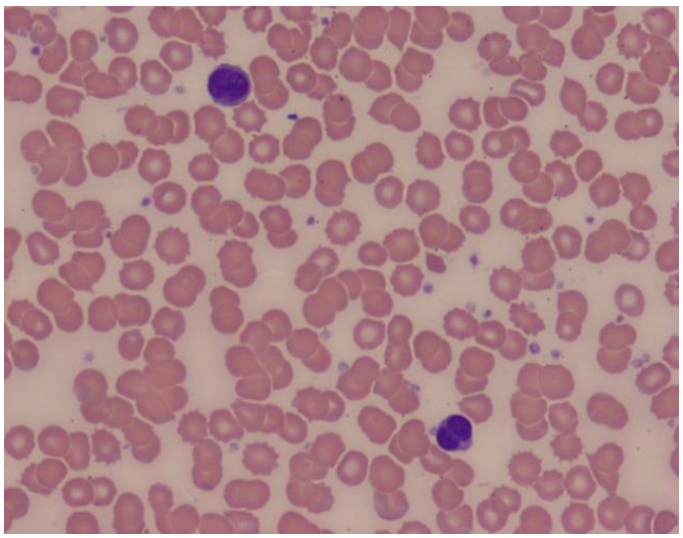

**Figure 2**. *Peripheral blood morphology, with a modified Wright's stain, showing characteristic Sézary cells with cerebriform nuclei which appear blue.*

approximately two months after his initial presentation to our dermatology clinic.

## Case Discussion

SS is defined by the triad of erythroderma, generalized lymphadenopathy, and the presence of neoplastic T-cells (Sézary cells) in the skin, lymph nodes, and peripheral blood. Criteria recommended for the diagnosis of SS include demonstration of a T-cell clone in the peripheral blood by molecular or cytogenetic methods, demonstration of immunophenotypical abnormalities (an expanded CD4+ T-cell population resulting in a CD4/CD8 ratio gre ater than 10 and/or aberrant expression of pan-T-cell antigens), and an absolute Sézary cell count of least 1000 cells/µl. Our patient's Sézary cell count was 9800 cells/µl, almost ten times the diagnostic minimum, demonstrating a substantial leukemic T-cell burden in the blood. Clinically, our patient presented with the rare finding of leonine facies and loss of eyebrows, which occurred because of intense dermal cellular infiltration (related to malignant infiltration or reactive change). The list of disorders which are associated with leonine facies accompanied by eyebrow loss is limited and this includes malignancy such as lymphoma and leukemia cutis [2, 3].

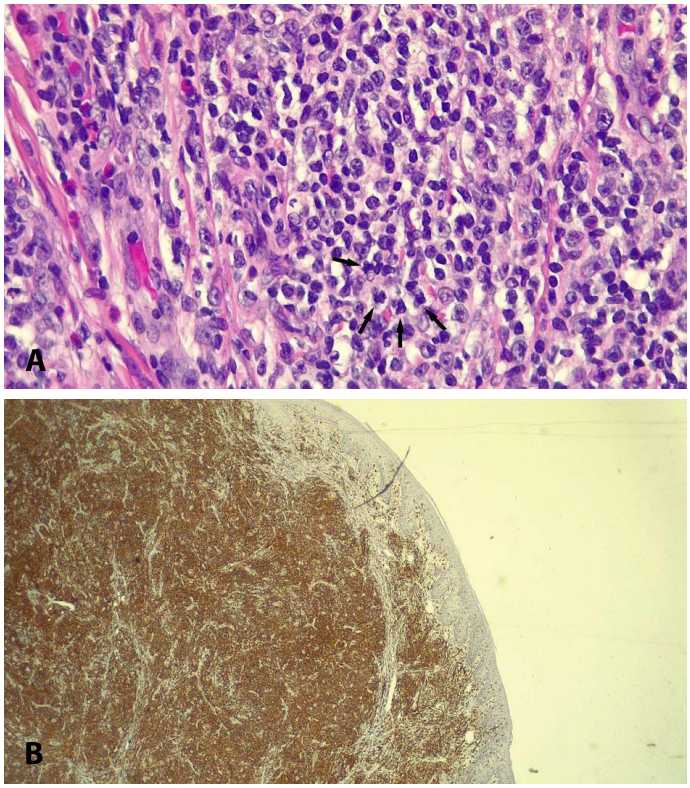


**Figure 3**. ***A)*** *A dense monomorphic lymphocytic dermal infiltrate, with arrows indicating several atypical neoplastic T-cells in the dermis. H&E, 20×.* ***B)*** *Immunohistochemical staining*

There are a few earlier case reports of MF and SS in the setting of HIV infection and HAART [4-7]. Several papers postulated possible mechanisms of development of cutaneous T-cell lymphoma (CTCL) in HIV positive patients. Burns and Cooper reported on two cases of MF in HIV positive patients; they concluded that in the absence of severe immunodeficiency, HIV-1-infected patients with concomitant CTCL may follow a more typical slowly progressive course [8]. Myskowski was one of the first authors to expand on the possible causes of CTCL development in the setting of HIV, including HIV itself and Epstein-Barr virus co-infection [9]. Berger et al. remarked that in the setting of CTCL and HIV, CD4 count may not be a useful marker to stage HIV disease; they further postulated that HIV itself may be capable of transforming T-cells, inducing lymphoma [10]. However, Rasmussen et al. more recently demonstrated that in an HIV-infected individual on HAART with SS, the malignant CD4+ T-cells were not infected with HIV and full-length sequencing of HIV-DNA demonstrated no clonal expansion in the non-malignant HIV-infected CD4+ T-cells [11].

It is known that multiple immune defects occur with progressive SS, resulting in altered cytokine expression pathways and impairment of cellular immunity [12]. Wysocka et al. demonstrated a direct association between the magnitude of circ ulating malignant T-cells and abnormalities in multiple components of the cellular immune response [13]. Enhanced T helper 2 (Th2) cytokine production occurs during disease progression, together with defects in T helper 1 (Th1) cytokine production [14]. There is an increase in $CD4^+/CCR4^+/CD26^-$ T-cells, as well as increased IL-4, IL-5, and IL-10 production. There is also a decrease in the number and function of circulating dendritic cells, $CD8^+$ T-cells, and $CD56^+$ NK cells. Decreased IL12, IFNα and IFNγ production occurs [12]; IL12 and IFNγ are important in anti-tumor surveillance. Increased numbers of regulatory

T-cells (Tregs) have also been implicated in the immune deficiency accompanying SS [15].

Yawalkar et al. found a profound reduction in the complexity of the T-cell repertoire in CTCL that in advanced disease is comparable to that seen in HIV-infected patients [16]. HIV infection itself leads to an impaired T-cell repertoire [17], a predominant Th2 immune response, and immune dysregulation. Lehloenya et al. reported a case of aggressive worsening of Sézary syndrome in the context of early HAART that they considered to be related to alterations in the dynamics of $CD4^+$ T-cell numbers and function induced by HAART [18]. Our patient was compliant with HAART and achieved HIV viral suppression, but the role HAART may have played in the development and progression of SS cannot be dismissed.

Although it is possible that our patient acquired HIV infection and SS separately, we postulate that two differing mechanisms may have led to these diseases occurring simultaneously. We postulate that HIV infection could have preceded the development of SS, and owing to the various HIV-associated immune aberrations, including impaired tumor surveillance, SS developed. Alternatively, our patient could have had early stage SS prior to HIV infection, which lowered his threshold for acquiring HIV owing to the associated immune alterations. This scenario is possible because a loss of T-cell receptor complexity may occur in some patients with very early disease (e.g. stage IA), though it is uniformly present in patients with stages III and IV disease [17].

Ultimately in our patient, the combined immune aberrations of HIV infection and SS led to overwhelming immune dysregulation, further progression of SS, and renewed expansion of HIV. Thus, a cycle was created perpetuating immune suppression. The increase in our patient's CD4 count was likely reflective of the immense number of circulating malignant $CD4^+$ T-cells (Sézary cells). The loss of viral suppression, as evidenced by the acute rise in his HIV viral load, was likely linked to his immune function deterioration.

## Conclusion

This case highlights the complex interplay between HAART, HIV infection, and SS. SS already portends a poor prognosis [19, 20] and co-diagnosis with HIV infection can be devastating. Testing for HIV is advised in all patients with suspected CTCL. Conversely, any HIV-positive patient with an unexpected increase in CD4 count during routine monitoring, especially in the setting of unusual skin findings, should alert the clinician to seek out lymphoma or leukemia.

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