CD4-Positive T-Cell Large Granular Lymphocytosis Mimicking Sézary Syndrome in a Patient With Mycosis Fungoides

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Summary: A white woman aged 65 years presented with a macular, nonscaly, nonpruritic, erythematous lesion on her right breast. Test results revealed histological features similar to lichenoid dermatitis and early-phase primary cutaneous T-cell lymphoma with a subtype of mycosis fungoides (MF). Despite topical therapy with steroids, her skin disease continued to progress, so she underwent polymerase chain reaction and gene mutation testing. Two missense mutations were detected. The overall findings supported a diagnosis of co-occurring, CD4-positive large granular lymphocytosis and stage IA MF. The patient continued to receive topical steroids and maintenance phototherapy, and her skin lesions completely resolved after 14 weeks of therapy. Approximately 5 years after her initial presentation, she was free of symptoms, cytopenia, and no skin lesions were present. CD4-positive, large granular lymphocytosis was persistent. This patient case — to our knowledge, the first of its kind — posed dilemmas of a diagnostic and therapeutic nature. Correctly staging the lymphoma helped to aid the diagnosis and can help prevent patients similar to the one in this case from receiving unnecessary therapy.

Introduction

CD4-positive T-cell large granular lymphocytosis is an entity distinguished from conventional, CD8-positive T-cell large granular lymphocytic leukemia (LGLL). LGLL is frequently associated with sustained cytopenia, autoimmunity, splenomegaly, and recurrent mucocutaneous infections; and it has immunophenotypical positivity for CD3, CD8, CD57, and T-cell receptor αβ. Other rare immunophenotypic variants (eg, T-cell receptor γδ) have also been reported. By contrast, CD4-positive large granular lymphocytosis is a clonal T-cell lymphoproliferative disorder often associated with various neoplastic or autoimmune disorders or emerging from an iatrogenic immunotherapy. Given the aberrant expression of “pan” T-cell markers in addition to CD57, including positivity for CD3, positivity for CD4, dim positivity and negativity for CD8, CD7-positive subset, CD56-negative subset, and positivity for T-cell receptor αβ, such a population could be misinterpreted as another mature T-cell lymphoma, especially when the patient lacks a clear clinical history or a clinical investigation is incomplete.

Herein, we discuss a clinical scenario that, to our knowledge, is the first such case report of sustained, CD4-positive large granular lymphocytosis occurring in a patient with stage IA mycosis fungoides (MF) that posed diagnostic and treatment dilemmas.

Case Report

A 65-year-old white woman initially noted a macular, nonscaly, nonpruritic, erythematous lesion on her right breast. The lesion subsequently became more papular in appearance, and several additional maculopapular lesions emerged on her back and abdomen. Findings on shave biopsy of the lesion on her back showed histological features similar to lichenoid dermatitis and early-phase primary cutaneous T-cell lymphoma with an MF subtype.

Findings on staging positron emission tomography were normal. Complete blood count showed a white blood cell count of 11.9 × 10^9/µL and an absolute lymphocyte count of 5535/µL (45%). A brief flow cytometry panel was performed on peripheral blood mononuclear cells and identified a partial loss of CD26 antigen on T-cell lymphocytes and aberrant expression of CD57 of uncertain clinical significance. Staging bone marrow biopsy showed a small population of T cells (15%) with a similar phenotype.

Findings on shave biopsy of another skin lesion located on her shin revealed atypical lymphoid cells with cerebriform nuclei in the epidermis, thus suggesting a diagnosis of MF. Peripheral blood flow cytometry revealed a distinct population of T cells positive for CD4, dimly positive for CD7, and negative for CD26 comprising approximately 61% of the gated lymphocytes with an ab-
absolute count of abnormal lymphocytes of 3544/µL. The lymphoid cells also expressed CD56, CD57, and T-cell receptor αβ, but they lacked positivity for CD16, CD25, CD30, HLA-DR, and T-cell receptor γδ (Fig 1). Examination of peripheral blood film showed that the majority of lymphocytes were large granular lymphocytes (Fig 2A–B). Serological test results for HIV and human T-cell lymphotropic virus were negative. Although atypical lymphoid cells with classic cerebriform nuclei were absent, differential diagnoses should include Sézary syndrome, reactive T-cell lymphocytosis, T-cell LGCL, peripheral T-cell lymphoma (leukemic phase), and blastic plasmacytoid dendritic cell neoplasm.

The patient was treated with topical steroids. After 4 months, the skin disease progressed, with patch disease and similar morphology and immunophenotype noted (Fig 2C–D). Repeat flow cytometry performed on her peripheral blood showed a population of atypical T cells (absolute count > 2000/µL) with unchanged immunophenotype.

Polymerase chain reaction (PCR) was used to identify the clonal TCR rearrangement. To target T-cell receptors in the Dβ, Jβ, Jγ, Vβ, and Vγ regions, PCR amplification was performed in 5 multiplex PCR tubes
with primers, after which the products were detected and separated using capillary gel electrophoresis on a genetic analyzer. Clonal TCR rearrangement was identified at peaks at 249.85 and 298.53, and clonal TCR γ rearrangement was visualized at peaks at 209.12 and 175.46 (Fig 3). Karyotyping performed on peripheral blood revealed a normal female karyotype.

Gene mutation testing was performed with the
NexCourse Complete (Genoptix, Carlsbad, CA) assay. This type of assay interrogates 173 genes known to be recurrently mutated in cancers, including T- and B-cell lymphoproliferative disorders (sequencing depth of 500 × coverage). The results showed no pathologically significant mutations (Fig 4), including the absence of STAT3 and STAT5B, which are frequently mutated in T-cell LGLL. Two missense mutations, CCNE1 112G>A, p.R374Q with 52% allele frequency and RAD21 1811A>G, p.K604R with 49% allele frequency, were detected. In our experience, both of these mutations have rarely been reported, and their clinical significance is uncertain.

The overall findings supported a diagnosis of CD4-positive large granular lymphocytosis — rather than Sézary syndrome — occurring simultaneously with advanced-stage MF.

The patient continued to receive topical steroids and then was switched to narrowband ultraviolet B phototherapy when new skin lesions developed. After 14 weeks of phototherapy, her skin lesions completely resolved. Subsequently, she continued receiving maintenance phototherapy. At her last follow-up visit approximately 5 years after her initial presentation, she had persistent, circulating CD4-positive T-cell large granular lymphocytosis (4460/µL) without any symptoms or cytopenia. No skin lesions were present.

**Discussion**

CD4-positive T-helper cells are a subtype of lymphocytes, major histocompatibility complex class 2 restricted, that play a key role in adaptive immunity. Of note, most cases of peripheral cell lymphoma originate from CD4-positive T cells. By contrast to CD4-positive mature lymphomas, CD4-positive large granular lymphocytosis is a laboratory finding with good clinical outcomes. The entity is considered rather to be a reactive than a neoplastic process and it has been found to be paraneoplastic, yet with an uncertain pathogenesis. In our experience, certain medication use, cytokine release, and immune dysregulation in response to an underlying primary neoplasm could trigger increased production of CD4-positive T lymphocytes.

Garrido et al showed the coexistence of the T-cell receptor Vβ repertoire (eg, positive for T-cell receptor Vβ13.1, HLA-DRB1*0701), suggesting that CD4-positive large granular lymphocytosis may originate from an antigen-driven, clonal T-cell stimulation. It is contro-

![Fig 3A–D. — Clonal TCR rearrangements were detected by polymerase chain reaction. (A) TCR β tube B. (B) TCR β tube C. (C) TCR γ tube A. (D) TCR γ tube B.](image-url)
versal as to whether CD4-positive large granular lymphocytosis with a benign course should be considered to be a variant of T-cell LGLL. STAT5B mutation is also frequently detected in CD4-variant T-cell LGLL, a finding that could be useful for subcategorizing the entity.9 Regardless, in our experience, the mainstay of treatment for CD4-variant T-cell LGLL is observation alone.

STAT5B mutations were not detected in our patient after targeted gene sequencing (see Fig 4), a finding that could be attributed to different technologies used for testing. Of note, Andersson et al9 used an exome-sequencing platform for detecting STAT5B mutation on sorted CD4-positive or CD4-positive/CD8-positive cells and used CD4-negative fractions as a control with higher sensitivity and specificity rates.

In our patient, lack of generalized lymphadenopathy diminished the likelihood of peripheral blood involvement by CD4-positive peripheral T-cell lymphoma, not otherwise specified.7 Blastic plasmacytoid dendritic cell neoplasm dually expresses CD4/CD56 that could mimic CD4-positive large granular lymphocytosis. However, blastic plasmacytoid dendritic cell neoplasm also co-expresses CD123, TCL1, or CD303 (BDCA2) and shows blastoid cytological features;9 these were negative in our patient.

Abnormal CD4-positive T-cell proliferation that coexisted with MF in our patient raised suspicion for Sézary syndrome as the diagnosis, because both cutaneous and peripheral circulating abnormal T cells shared a similar phenotype: CD4 positivity with loss of CD7 and CD26.11 However, these CD4-positive cells also express CD57 and CD56, thus mitigating a diagnosis of Sézary syndrome. Furthermore, the patient never presented with the classic skin manifestations associated with Sézary syndrome (eg, exfoliative erythroderma).

Conclusions

The patient in our case had an unusual clinical presentation with concurrent stage IA mycosis fungoides and sustained, CD4-positive large granular lymphocytosis. An accurate diagnosis can aid clinicians in correctly staging lymphoma and can help prevent patients similar to ours from receiving unnecessary therapy.

References