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Case study

A unique CD4$^+$ large granular lymphocytosis occurring in patients treated with tumor necrosis factor α inhibitors: report of 2 cases

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Summary We report 2 cases of CD4$^+$ large granular lymphocyte (LGL) lymphocytosis occurring in patients being treated with a monoclonal antibody against tumor necrosis factor α for underlying autoimmune disorders. CD4$^+$ LGL lymphocytosis is a rare subset of LGL disease that has previously only been described in patients without underlying autoimmune disorders, and most demonstrate uniform coexpression of CD56 on the atypical T cells. The clinical features, with both cases occurring in patients with autoimmune disease, and immunophenotypic features, with both cases showing dim CD8 coexpression without CD56 in the CD4$^+$ LGLs, suggest that the reported cases are distinct from those previously described and may represent a novel T-cell LGL lymphocytosis emerging from iatrogenic immune modulation of patients with underlying autoimmune disorders.

1. Introduction

T-cell large granular lymphocytic (T-LGL) leukemia is a relatively uncommon, indolent hematologic malignancy characterized by a persistent clonal expansion of peripheral blood large granular lymphocytes (LGLs) with a cytotoxic CD8$^+$ T-cell immunophenotype. In contrast, rare cases of T-LGL proliferations composed of monoclonal CD4$^+$ T cells with dim or no coexpression of CD8 (CD4$^+$ T-LGL leukemia) are also described [1-5]. From 2 case series with a total 42 patients, CD4$^+$ T-LGL lymphocytosis appears to have clinicopathological features that are distinct from classic CD8$^+$ T-LGL leukemia, with almost all patients lacking the cytopenias or the association with autoimmune disease frequently seen in classic CD8$^+$ T-LGL leukemia and with many patients harboring secondary malignancies [1,2].

We present 2 unusual cases of CD4$^+$ T-LGL lymphocytosis with dim CD8 coexpression that deviate from this reported clinicopathological presentation, both occurring in patients with autoimmune disorders, 1 with severe neutropenia, and, to date, neither patient having been found to have an underlying secondary malignancy. Interestingly, both patients were being treated with a monoclonal antibody against tumor necrosis factor α (TNF-α) at the time of diagnosis.

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Table Patient characteristics

	Case 1	Case 2
Sex	Male	Female
Age (y)	74	54
Autoimmue disorder	Seropositive rheumatoid arthritis	Polyarthralgia, spondylarthopathy, HLA-B27 positive
Splenomegaly	No	No
Adenopathy	No	No
CBC at diagnosis		
WBC	12 800/μL	8900/μL
ANC	260/μL	3800/μL
ALC	12 290/μL	4260/μL
Hgb	13.7 g/dL	14.3 g/dL
PLT	122 K/μL	249 K/μL
Peripheral smear	Numerous LGLs	Polymorphous lymphocytes with occasional LGLs
T-LGL immunophentype	$CD4^+$, $CD8^{dim}$, $CD5^{dim}$, $CD7^{dim}$, $CD16^-$, $CD56^-$, $CD57^+$	$CD4^+$, $CD8^{dim}$, $CD5^+$, $CD7^{dim}$, $CD16^-$, CD56 largely negative, CD57 largely negative
$CD4^+/CD8^{dim}$ T cells	6913/μL	766/μL
TCRγ rearrangement by PCR	Not performed	Monoclonal amplicon present within a polyclonal background
Adalimumab treatment duration	12 y	4 mo
Therapy and response	Discontinuation of adalimumab and subsequent initiation of methotrexate resulted in ANC of 1260/μL and ALC of 6370/μL	Discontinuation of adalimumab resulted in ALC of 2913/μL and absolute $CD4^+/CD8^{dim}$ T cells of 572/μL

Abbreviations: CBC, complete blood count; WBC, white blood cell; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; Hgb, hemoglobin level; PLT, platelet; TCRγ, T-cell receptor γ; PCR, polymerase chain reaction; LGL, large granular lymphocyte.

2. Report of cases

2.1. Case 1

A 74-year-old man was found to have neutropenia (absolute neutrophil count [ANC], 260/μL), lymphocytosis (absolute lymphocyte count [ALC],12 290/μL), and thrombocytopenia (122 K/μL) on a routine visit. He was diagnosed with rheumatoid arthritis 19 years before presentation, and for 10 years, his arthralgias were well controlled with a combination of 5 mg of oral methotrexate per week and 40 mg of subcutaneous adalimumab every 14 days. In an effort to decrease his medications 2 years before presentation, methotrexate was discontinued, and adalimumab was administered every 3 weeks, with good symptomatic control.

On physical exam, the patient was afebrile and did not have any synovitis, joint deformity, mucocutaneous ulcers, or rashes. No adenopathy or splenomegaly was appreciated. The peripheral smear showed a marked lymphocytosis composed predominantly of LGLs. Flow cytometry performed on his peripheral blood showed that 75% of the total lymphocytes were atypical T cells that coexpressed CD4 with dim CD8, dim CD5, dim CD7, and CD57 without CD16 or CD56 (Table and Fig. 1). Interestingly, a small population of dim CD8 T cells lacking CD4, with otherwise identical antigen expression patterns as the predominant $CD4^+/CD8^{dim}$ T cells, was also detected (Fig. 1), likely representing a subclonal population.

Two months after adalimumab was discontinued, the patient developed some mild arthralgias, and his ANC had risen minimally to 560/μL, whereas his ALC remained at 11 650/μL (Fig. 2). Methotrexate 20 mg per week was restarted in an effort to treat both the rheumatoid arthritis and T-LGL lymphocytosis. After 6 months of treatment, the patient's ANC rose to 1260/μL, and ALC decreased to 6370/μL. To date, no underlying secondary malignancy has been diagnosed.

2.2. Case 2

A 54-year-old woman was found to have mild lymphocytosis (ALC, 4260/μL) on routine monitoring laboratories. The patient had multiple medical problems including polyarthralgia, complex pain syndrome, and an HLA-B27–related spondyloarthropathy. A trial of adalimumab was initiated 4 months before her presentation, which resulted in some improvement of her joint and back pain. Approximately 9 months before presentation, the patient was hospitalized for a suspected viral illness associated with neutrophilia and lymphocytosis that resolved within 48 hours (Fig. 2).

On physical exam, the patient was afebrile, no rashes were seen, and no adenopathy or splenomegaly was appreciated. With the exception of the mild absolute lymphocytosis, her blood counts were otherwise entirely normal, without anemia or thrombocytopenia (Table). The peripheral smear showed a mixture of leukocytes including normal-appearing neutrophils, small mature lymphocytes, and occasional LGLs. Flow cytometry performed on the peripheral blood showed a mixed population of T cells, 54% of which expressed CD4. Thirty-four percent of the $CD4^+$ T cells, or 23% of the total T cells (766/μL), coexpressed dim CD8, dim CD7, largely negative CD56, and largely negative CD57, without CD16 (Table and Fig. 1).