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Autoimmune and inflammatory diseases associated with T-cell clonal expansion

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Running head: Autoimmune disease and T-cell clonality

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Disclosure of Conflicts of Interest

The authors declare no conflicts of interest.

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Abstract

Autoimmune and inflammatory diseases (AID) result from a breakdown of immune tolerance, often driven by T-cell dysregulation and sometimes associated with clonal T-cell expansion. While T-cell large granular lymphocyte leukemia (LGL-L) is a well-defined clonal disorder commonly associated with AID, the clinical relevance of T-cell clones of uncertain significance (T-CUS) remains unclear. We conducted a retrospective multicenter study across six French centers, including patients with persistent circulating clonal T cells associated with AID, confirmed by T-cell receptor gene rearrangement. T-cell clones $\geq 0.5 \times 10^9/L$, or low-count clones ($<0.5 \times 10^9/L$) associated with rheumatoid arthritis, unexplained cytopenias, or compatible bone marrow infiltration, were classified as LGL-L. T-CUS was defined by exclusion in patients who did not fulfill diagnostic criteria for T-LGL leukemia. Eighty-three patients were included (44 LGL-L and 39 T-CUS). LGL-L patients predominantly exhibited a CD8⁺ phenotype (66%) and *STAT3* mutations (54%), and were more frequently associated with rheumatoid arthritis (41% vs 0%, $p<0.0001$) and neutropenia (52% vs 5%, $p<0.0001$), compared to patients with T-CUS. Granulomatous diseases were more common in the T-CUS group (28% vs 5%, $p<0.01$), which also displayed a broader and more heterogeneous autoimmune spectrum and a higher frequency of *TET2* mutations (27% vs 0%, $p<0.01$). Response to T-cell targeted therapy was similar between the two groups. Overall, these findings indicate that T-cell clonality in the context of AID encompasses heterogeneous entities, ranging from reactive immune phenomena to grey-zone clones sharing features with LGL-L, supporting an integrated clinical, immunophenotypic, and molecular approach to patient management.

INTRODUCTION

Autoimmune and inflammatory diseases (AID) are a heterogeneous group of conditions ranging from organ-specific disorders to systemic diseases.¹ They are primarily linked to a breakdown in immune self-tolerance, driven by environmental triggers and genetic predisposition. T-cells play a central role in maintaining immune homeostasis and act as key effectors in the development of autoimmunity.² Under chronic antigenic stimulation, such as neoplasia, infection, transplantation, autoimmunity, or aging, restricted T-cell clonal expansions may emerge.^{3,4} These clones may exhibit perfect similarities to those that support the diagnosis of large granular lymphocyte leukemia (LGL-L): a chronic clonal lymphoproliferative disorder often associated with autoimmunity and cytopenias.⁵ In LGL-L, an autoimmune condition is present in approximately 25–33% of cases, among which rheumatoid arthritis (RA) and pure red cell aplasia (PRCA) are the most frequent.^{6–8} The diagnosis relies on a persistent clonal LGL population $\geq 0.5 \times 10^9/L$ with a compatible phenotype, clonality being assessed either by TRBC1 expression or T-cell receptor (TCR) rearrangement for T-LGL-L.⁹ Lymphoid next-generation sequencing (NGS) analysis is also useful for diagnostic purposes, as *STAT3* gain-of-function mutations are frequently reported in LGL-L.^{10,11}

In contrast, T-cell clone of uncertain significance (T-CUS) refers to a persistent oligo or monoclonality in the absence of clinical or biological features that would allow the diagnosis of LGL-L. T-CUS shares molecular and immunophenotypic characteristics with LGL-L, yet individuals carrying these abnormal clones show no clinical or laboratory evidence indicative of a T-cell malignancy, and the clonal T-cell count is often below the threshold of $0.5 \times 10^9/L$.^{12–14} Overall, with the growing use and improvement of techniques like flow cytometry and TCR gene rearrangement, clonal T-cell populations are increasingly identified in routine clinical practice. Recent studies describe clonal LGL-L disorders as a continuum from reactive clonal expansion to aggressive LGL-L. Within this spectrum, an intermediate grey zone exists between T-CUS and indolent LGL-L, where overlapping clinical, immunophenotypic, and molecular features make the distinction between these two entities difficult.^{9,12}

To date, no validated monitoring strategies or therapeutic guidelines exist for AID associated with T-CUS. An important question is whether treatments commonly applied in LGL-L should also be considered in this context. Thus, we conducted a retrospective study with the aim of better specifying the spectrum of AID encountered during the course of clonal T-cell expansions. We specifically included patients with AID associated with T-CUS or LGL-L, in order to compare their clinical, biological, and therapeutic characteristics. Ultimately, we also aimed to provide tools for effective interpretation and management of patients with T-cell clonality in the context of AID.

METHODS

Study design:

We conducted a retrospective, multicenter cohort study in 6 French centers: Le Mans Hospital, University Hospital Center of Cochin, Angers, Nantes, Marseille, Toulouse, and through a national call for cases.

Eligibility criteria

Patients were eligible for inclusion if they met all of the following criteria: (i) the presence of a documented AID, (ii) detection of T-cell expansion by flow cytometry and (iii) confirmation of a monoclonal T-cell population demonstrated by either T-cell receptor (TCR) gene rearrangement analysis or TRBC1 flow cytometry. To limit the inclusion of transient or reactive clonal expansions, confirmation of T-cell clonality within a three-month interval was required.

Patients with NK-cell proliferations were excluded from the final analysis to focus specifically on T-cell clonal expansions. Patients with overt T-cell malignancy at inclusion, such as aggressive T-cell lymphomas or T-cell chronic leukemias different from LGL-L according to the 2022 World Health Organization (WHO) classification, were also excluded.

Patient recruitment and data collection:

Patients were recruited through multiple complementary approaches. A call for participation was distributed by email within each participating center to relevant specialists, including internists, hematologists, nephrologists, and rheumatologists. Patients with an associated AID and T-cell expansion documented in their medical records were then selected. Data were collected between 2011 and 2024 across six participating centers, with additional cases identified through a national call for cases.

When available, lymphoid NGS data were collected, including analyses of *STAT3* and *STAT5B* mutations. Demographic characteristics (age and sex), biological parameters (blood cell counts), and treatment-related data were recorded, including the use of corticosteroids and immunosuppressive agents, as well as treatment outcomes. Treatment response was retrospectively assessed according to the treating physician's evaluation of AID activity and classified as complete remission, partial remission, or treatment failure based on clinical and/or biological improvement.

Ethical approval:

This study was approved by the local ethical committee of Le Mans Hospital (N°2023-014). Data collection was pseudonymized, and each patient was informed by a non-opposition letter sent directly to their personal postal address.

Diagnostic criteria:

All these patients presented with concomitant AID. Patients were then classified into two groups: LGL-L and T-CUS. LGL-L was defined according to the 2022 WHO classification and established expert recommendations^{5,9,15}, while T-CUS was classified based on published expert criteria.¹²

Patients with an LGL count $\geq 0.5 \times 10^9/L$ and a compatible immunophenotype were classified as LGL-L. Patients with a lower LGL count ($< 0.5 \times 10^9/L$) who fulfilled the grey-zone diagnostic criteria, defined by the presence of unexplained cytopenias, rheumatoid arthritis, or compatible bone marrow infiltration, were also classified as LGL-L. Patients with a clonal T-cell expansion who did not meet any of the above criteria were classified as T-CUS.

Each case was independently reviewed by an expert to assess patient classification.

Neutropenia was defined as an absolute neutrophil count $< 1.5 \times 10^9/L$, anemia as hemoglobin (Hb) < 11 g/dL, thrombocytopenia as a platelet count $< 150 \times 10^9/L$, lymphopenia as an absolute lymphocyte count (ALC) $< 1 \times 10^9/L$, and lymphocytosis as ALC $> 4 \times 10^9/L$.

Auto-immune and auto-inflammatory diseases:

We categorized the spectrum of AID present in the cohort for analysis. Each patient's conditions were grouped into one or more of the following groups: connective tissue diseases, biopsy-proven granulomatosis (sarcoidosis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis and granulomatous inflammation related to immune deficiency), RA, idiopathic pulmonary hypertension, autoimmune cytopenias, autoinflammatory diseases, inflammatory bowel diseases (IBD)/ankylosing spondylitis (AS), primary immune deficiency (PID), vasculitis, hypereosinophilic syndrome (HES), endocrinopathies, antiphospholipid syndrome (APS) and other disease. Of note, different AID could coexist in the same patient.

Statistical analysis:

Data were reported as numbers (n) and percentages (%) for categorical variables, compared using the Chi-square or Fisher's exact test as appropriate. For continuous variables, Welch's t-test was used to compare means when data were normally distributed but variances were unequal, whereas the Mann-Whitney U test was used for non-normally distributed data. Variables included in the model were selected based on clinical relevance and univariate analysis results. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. A p-value < 0.05 was considered statistically significant. Event-free survival, defined as the time to next treatment, relapse, or death, was estimated using the Kaplan-Meier method, and differences between groups were assessed with the log-rank test. Statistical analyses were performed with GraphPad Prism.

RESULTS

Patient data:

A total of 147 patients were screened for eligibility. Overall, 83 patients with a T-cell clone and AID met the inclusion criteria and were included in the analysis. Thirty-nine patients (47%) were classified in the T-CUS/AID group and 44 patients (53%) in the LGL-L/AID subgroup (Figure 1). Neutropenia and lymphocytosis were the main indications for immunophenotyping in the LGL-L group (48% vs 2%, $p < 0.0001$, and 29% vs 5%, $p < 0.01$, respectively). Conversely, lymphadenopathy or organomegaly was the leading indication in the T-CUS group (31% vs 4%, $p < 0.01$), followed by general symptoms (20% vs 11%, $p = 0.25$). Otherwise, baseline characteristics were similar in the two groups (Table 1).

Biological, immunophenotyping, and molecular findings:

Neutropenia (52% vs. 5%, $p < 0.0001$) and lymphocytosis (34% vs. 8%, $p < 0.01$) were significantly more frequent in LGL-L patients than in T-CUS patients. The median value of the clonal T-cell population was significantly higher in the LGL-L group ($0.87 \times 10^9/L$, vs. $0.23 \times 10^9/L$, $p < 0.0001$) (Table 1). In LGL-L, $CD3^+CD4^-CD8^+$ cytotoxic T-cell phenotype was predominantly observed (66% vs. 36%, $p < 0.01$; often associated with co-expression of CD57), while T-CUS patients tended to display non-cytotoxic or atypical phenotypes, such as $CD3^+CD4^-CD8^-$ (31% vs. 14%, $p = 0.06$) and $CD3^-CD4^+CD8^-$ (10% vs. 0%, $p < 0.05$). The distribution of TCR $\alpha\beta$ and TCR $\gamma\delta$ clones was similar between groups (Table 2). Of note, four patients with a low-count T-cell clone ($< 0.5 \times 10^9/L$) associated with neutropenia and/or RA were included in the LGL-L group, as they fulfilled the criteria for the grey zone profile. Conversely, one patient with a T-cell clone $\geq 0.5 \times 10^9/L$ was classified as T-CUS because of an atypical immunophenotype ($CD3^-CD4^+CD8^-$) consistent with the classical T-cell clone described in context of HES.

Thirty-seven out of the 83 (45%) patients underwent NGS, 26 in LGL-L and 11 in T-CUS subgroups, respectively. *STAT3* mutations were detected in 54% of patients with LGL-L, whereas none of the patients with T-CUS harbored *STAT3* variants ($p < 0.01$). Two patients in the LGL-L group, including one with a $CD4^+$ phenotype, harbored a *STAT5B* mutation, compared with one patient in the T-CUS group. *TET2* mutations were rarely detected and found only in the T-CUS group (27% vs 0%, $p < 0.01$) (Figure 2).

The spectrum of autoimmune and inflammatory diseases associated with T-CUS and LGL-L:

The mean number of AID per patient was 1.72 with no significant difference between patient subgroups (1.77 vs. 1.46 in LGL-L and T-CUS subgroups, $p = 0.08$).

Rheumatoid arthritis (41% vs. 0%, $p < 0.0001$) was more frequent in LGL-L patients. Connective tissue diseases also tended to be more frequent in LGL-L patients, although the difference did not reach statistical significance (20% vs. 13%, $p = 0.35$). Conversely, granulomatous diseases were more frequently reported in the T-CUS group (28% vs. 5%, $p < 0.01$) (Table 3). Although not statistically significant, there was a trend towards a higher rate of both vasculitis (20% vs. 7%, $p = 0.06$) and HES (15% vs. 5%, $p = 0.14$) in this group. In this line, all four patients with ANCA-associated vasculitis (AAV) belonged to the T-CUS group (Table S1). Likewise, all cases of PID ($n=4$) and of retroperitoneal fibrosis (RPF, $n=2$) were reported in the T-CUS group. Lastly, the rates of autoimmune cytopenia did not differ between patient subgroups (Figure S3).

Notably, some hematological malignant and premalignant comorbidities were observed in 23% and 26% in LGL-L and T-CUS groups, respectively. Detailed results are provided in supplementary Table S2.

Treatments and outcomes:

Among the 83 patients included in the cohort, 78% ($n=65$) received at least one line of treatment. Treatment was exclusively initiated for AID in all treated T-CUS patients, whereas neutropenia was an indication for treatment in 38% of LGL-L patients, compared with none of the T-CUS patients ($p<0.001$). Among treated patients, glucocorticoid use was more frequent in the T-CUS group than in the LGL-L group (100% vs. 81%, $p < 0.05$), whereas the use of immunosuppressants was comparable between the T-CUS and LGL-L patients (79% vs. 92%, $p=0.12$). Across all therapeutic lines, T-cell targeted therapy, including methotrexate, cyclosporine, cyclophosphamide, azathioprine, and mycophenolate mofetil, was used in 30 patients of the LGL-L group and 19 patients of the T-CUS group ($p=0.22$). Among patients who received T-cell targeted therapy, methotrexate was used more frequently in LGL-L than in T-CUS (70% vs 32%, $p<0.01$). The use of second-line therapy was not different in the two groups, with a median of two therapy lines (Table 4).

Response rates to glucocorticoids were similar between the two groups, with complete and partial responses being reported in 21% vs. 30% ($p=0.55$) and 71% vs 63% ($p=0.58$) of cases in T-CUS and LGL-L patients, respectively. Among first-line treatments (glucocorticoids, T-cell-targeted therapies, and other immunosuppressants), glucocorticoids achieved the highest response rates, reaching 92% in T-CUS group ($p < 0.001$) and 93% in LGL-L group ($p < 0.01$).

In patients who received first-line immunosuppressive therapy (22 T-CUS and 34 LGL-L), response rates were similar between T-CUS and LGL-L, with 50% of patients achieving complete remission in each group.

Treatment failure after first-line T-cell target therapy was observed in 48% of patients in LGL-L group and in 38% in T-CUS group ($p=0.73$). In comparison, failure rates with other immunosuppressive agents reached 56 % in T-CUS and 71 % in LGL-L ($p=0.47$) (Table S3). Overall, response to T-cell-targeted therapy did not differ between the two groups.

During the available follow-up period, no progression from T-CUS to overt T-LGL leukemia was observed. At the time of inclusion, seven patients had died (8%) with no significant difference between groups (4 in the T-CUS group and 3 in the LGL-L group; $p = 0.7$) (Table 4). Event-free survival was similar in both groups. The curves initially favored LGL-L but converged over time, with similar event-free proportions at 52 weeks and no significant difference ($p = 0.61$, Figure S1).

DISCUSSION

In this retrospective study, we tried to elucidate the clinico-epidemiological differences observed in patients presenting with AID associated either with LGL-L or T-CUS. To our knowledge, this is the largest reported cohort of patients with AID and concomitant T-cell clonality, and the first specifically comparing AID spectrum between T-CUS and T-LGL leukemia.

Our findings demonstrate distinct phenotypic differences between these two closely related conditions. In particular, rheumatoid arthritis was the most frequent AID associated with LGL-L, consistent with previous studies reporting RA in up to 10–18% of LGL-L patients.^{6,7} In our cohort, the prevalence reached 41%, which is higher than previously reported and likely reflects a selection bias, as all LGL-L patients included in this study had concomitant AID. Rheumatoid arthritis often precedes the onset of LGL-L and may contribute to the clonal expansion.⁸

Then, granulomatous diseases were significantly more prevalent in the T-CUS group. This is in line with the literature, as no case of sarcoidosis has been reported yet in the setting of LGL-L, whereas T-cells are involved in the pathogenesis of sarcoidosis. Indeed, activated CD4+ T cells, particularly Th1 and Th17 subsets, drive granuloma formation and persistence through proinflammatory cytokines, while impaired regulatory T-cell function further contributes to uncontrolled inflammation.¹⁶ Moreover, previous studies using flow cytometry have described elevated $\gamma\delta$ T cells in peripheral blood of patients with active sarcoidosis, particularly in those with Scadding stage III disease or long-term disease evolution. However, in these reports, $\gamma\delta$ T-cell levels showed no correlation with serum angiotensin-converting enzyme levels and were rarely detected in bronchoalveolar lavage fluid or biopsy specimens, suggesting that these cells are not involved in granulomatous inflammation.^{17,18} Interestingly, four of eight sarcoidosis cases harbored a $\gamma\delta$ T-cell clone (Figure S2), suggesting that these expansions may reflect antigen-driven immune responses in sarcoidosis, although their pathological significance remains unclear. In this line, the higher frequency of lymphadenopathy observed in T-CUS may reflect chronic immune activation associated with the underlying AID, particularly in the context of the high prevalence of granulomatous diseases in this group. Importantly, this finding did not appear to indicate progression to overt T-cell lymphoma. Otherwise, in our cohort, AAV were only reported in the T-CUS group, which is concordant with the previous LGL-L cohorts describing cryoglobulinemia and livedoid vasculitis but no AAV.^{6,9,19} Beyond these associations, the remaining AID associated with T-CUS were more heterogeneous, as reflected by the higher number of patients classified in the “other diseases” category, covering eleven

unclassified or unclear conditions. This observation suggests that T-CUS may represent bystander events in the context of autoimmunity.

Immunological and biological features further supported the distinction between the two groups. Indeed, neutropenia was markedly more frequent in LGL-L, concordant with previous reports showing a prevalence of 70-85%⁶ and sustained by pathophysiological link.^{20,21}

In addition, the LGL-L group exhibited a significantly higher proportion of CD8⁺ T cells and increased CD57 expression, reflecting a terminal effector-memory phenotype with potent cytotoxic activity driven by chronic antigenic stimulation, a hallmark of LGL-L pathophysiology.⁸

The mutational landscape also differed between groups. The genetic and molecular profile of LGL-L has recently been characterized, with more than 75% of patients harboring recurrent mutations. *STAT3* mutations occur in up to 60% of T-LGL leukemia and 30% of NK-LGL leukemia cases, whereas *TET2* mutations are predominantly found in NK-LGL leukemia around 30% and less frequent in T-LGL leukemia.^{22,23} In our cohort, *STAT3* mutations were restricted to LGL-L, consistent with previous reports showing no *STAT3* mutations in T-CUS to date. However, because mutational status was available for only 45% of the cohort, the prevalence of *STAT3* mutations in LGL-L was likely underestimated. *STAT3* mutation promotes apoptosis resistance and a more cytotoxic phenotype, frequently associated with severe cytopenias and RA^{8,24}, consistent with our findings, as 11 of the 14 *STAT3*-mutated patients had RA. Among the two LGL-L patients with a *STAT5B* mutation, one had CD4⁺ T-LGL leukemia, consistent with previous reports describing this mutation in established T-LGL leukemia, particularly in the CD4⁺ subtype.^{25,26} Conversely, *TET2* mutations were observed only in T-CUS. The absence of *TET2* mutations in LGL-L group differs from previous reports^{22,23} and likely reflects the limited availability of NGS data. Mutations in the epigenetic regulator *TET2* are associated with clonal hematopoiesis of indeterminate potential (CHIP), an age-related condition characterized by a pro-inflammatory environment, favoring clonal expansion and transformation in myeloid neoplasms.²⁷ *TET2*-mutated clones are also reported in T-follicular helper cell lymphomas, including 47% of angioimmunoblastic T-cell lymphomas.^{28,29} These findings raise the question of whether T-CUS represents a pre-leukemic step. In this regard, T-CUS may represent the T-cell counterpart of monoclonal gammopathy of uncertain significance (MGUS) or monoclonal B-cell lymphocytosis (MBL), two premalignant conditions often associated with autoimmunity. However, unlike MGUS and MBL, whose natural history and management are well established, T-CUS remains poorly characterized because of the lack of longitudinal studies.^{30,31}

Interestingly, we also identified other hematological premalignant or malignant conditions in 24% of patients, similar to previous LGL-L series.³² Notably, the co-occurrence of LGL-L with myelodysplastic syndrome (MDS) suggests a shared pathogenic background and possibly a common clonal origin supported by overlapping mutational landscapes.^{33–35} Likewise, T-CUS expansions have been described in MDS, where clonal cytotoxic CD8⁺ T cells contribute to

ineffective hematopoiesis, as suggested by responses to immunosuppressive therapies such as cyclosporine.^{36,37} One T-CUS patient also harbored an *UBA1* mutation in the context of VEXAS syndrome, a condition frequently associated with MDS.³⁸ Together, these findings suggest that T-CUS may contribute to an inflammatory bone marrow microenvironment and potentially participate in the evolution toward myeloid neoplasms.

Regarding treatment, glucocorticoids were more frequently used in T-CUS, likely reflecting the predominance of AID in guiding treatment decision in this group, and were effective in both groups. In contrast, methotrexate, a standard first-line therapy for LGL-L^{9,15}, was used more frequently in LGL-L, mainly for neutropenia. Although the role of T-cell-targeted therapies in T-CUS remains unclear, remission rates were similar between groups, raising the possibility that the T-cell clone contributes to disease activity, analogous to monoclonal gammopathy of clinical significance (MGCS), in which B-cell- or plasma cell-directed therapy may be indicated despite the absence of overt malignancy.³⁹ However, these findings should be interpreted cautiously, as treatment indications differed between the two groups: neutropenia prompted treatment in 38% of LGL-L patients but in none of the T-CUS patients. Moreover, treatment response was assessed only according to AID activity or neutropenia improvement, and the retrospective design precluded assessment of changes in clonal T-cell burden; therefore, no conclusions can be drawn regarding the impact of T-cell-targeted therapies on the clone itself.

The strengths of this study include its original multicenter cohort comparing LGL-L and T-CUS with AID, with centralized review by an LGL-L expert ensuring consistent diagnostic classification. However, its retrospective design introduced inherent selection and information biases. Restricting inclusion to patients with concomitant AID may also limit the generalizability of our findings to unselected LGL-L and T-CUS populations. Additionally, fewer than half of patients underwent NGS, limiting the analysis of somatic mutations, and AID classification relied solely on clinicians' reports without independent validation. Although no progression from T-CUS to overt T-cell malignancy was observed during follow-up, the retrospective and cross-sectional design precluded evaluation of long-term evolution.

Distinguishing T-CUS from indolent LGL-L remains challenging, because both entities likely form a biological continuum with an overlapping grey zone. This overlap suggests that clone size alone is insufficient to assess the clinical relevance of T-cell clonality, emphasizing the need to integrate clinical features, immunophenotype and somatic mutations into risk stratification and therapeutic decision-making. T-CUS should therefore be viewed as a spectrum, ranging from benign or reactive clonal expansions to clones sharing biological features with LGL-L and capable of progression. Accordingly, patients fulfilling grey-zone diagnostic criteria were classified as LGL-L, as these cases more likely represent early LGL-L than true T-CUS. This biological continuum also raises questions

regarding the mechanisms driving clonal emergence and progression. Causality is likely bidirectional: chronic inflammation may promote T-cell clonal expansion, yet certain autoimmune disorders themselves are recognized lymphoma risk factors⁴⁰, indicating that autoimmunity can both drive and result from clonal evolution.

In conclusion, our study highlights the broad and heterogeneous autoimmune spectrum associated with T-CUS and underscores the need for prospective longitudinal studies to identify patients at risk of progression and define appropriate surveillance strategies.

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TABLES AND FIGURES

Table 1: Demographic and biological characteristics of patients

	T-CUS (n=39)	LGL-L* (n=44)	Total (n=83)	p-value
Age (yr), median (IQR)	63 (43-73)	67 (61-73)	66 (50-73)	<0.05
Sex				
Female, n (%)	16 (41%)	27 (62%)	43 (52%)	0.06
Neutropenia (<1.5 ×10⁹/L), n (%)	2 (5%)	23 (52%)	25 (30%)	<0.0001
Anemia (< 11 g/dL), n (%)	10 (26%)	13 (29%)	23 (27%)	0.69
Thrombocytopenia (<150 ×10⁹/L), n (%)	9 (23%)	9 (20%)	18 (22%)	0.78
Lymphopenia (< 1 ×10⁹/L), n (%)	8 (20%)	2 (4%)	10 (12%)	<0.05
Lymphocytosis (> 4 ×10⁹/L), n (%)	3 (8%)	15 (34%)	18 (22%)	<0.01
Clonal T-cell count, (×10⁹/L) median (IQR)	0.23 (0.14-0.35)	0.87 (0.60-1.38)	0.47 (0.2-0.9)	<0.0001
Time between T-cell clonality detection and AID (months), median (IQR)	18 (8-60)	36 (9-150)	24 (8-87)	0.2
T-cell clonality before diagnosis of AID, n (%)	3 (8%)	7 (16%)	10 (12%)	0.17
Number of autoimmune diseases per patient, mean (SD)	1.46 (0.8)	1.77 (0.9)	1.72 (0.9)	0.08

*Including four patients considered as grey zone (low-count LGL) cases

AID: Autoimmune disease, IQR: Interquartile range, LGL-L: large granular lymphocyte leukemia, SD: Standard deviation, T-CUS: T-cell clonality of uncertain significance

Table 2: Immunophenotypic features of T-cell clones in the cohort

Clonal population, n (%)	T-CUS (n=39)	LGL-L* (n=44)	Total (n=83)	p-value
CD3 ⁺ / CD4 ⁻ /CD8 ⁺	14 (36%)	29 (66%)	43 (52%)	<0.01
CD3 ⁺ / CD4 ⁺ /CD8 ⁻	6 (15%)	5 (11%)	11 (13%)	0.48
CD3 ⁺ / CD4 ⁺ /CD8 ⁺	3 (8%)	4 (9%)	7 (8%)	1
CD3 ⁺ / CD4 ⁻ /CD8 ⁻	12 (31%)	6 (14%)	18 (22%)	0.06
CD3 ⁻ / CD4 ⁺ /CD8 ⁻	4 (10%)	0 (0%)	4 (5%)	<0.05
γδ	9 (23%)	6 (14%)	15 (18%)	0.26
αβ	32 (82%)	39 (89%)	71 (86%)	0.39
CD57	8 (21%)	19 (43%)	27 (33%)	<0.05
CD56	11 (28%)	22 (50%)	33 (40%)	<0.05
CD16	8 (20%)	10 (23%)	18 (22%)	0.8
CD2	20 (51%)	26 (59%)	46 (55%)	0.4
CD5	18 (46%)	19 (43%)	37 (45%)	0.47
CD7	18 (46%)	23 (52%)	41 (49%)	0.57

*Including four patients considered as grey zone (low-count LGL) cases

LGL-L: large granular lymphocyte leukemia, T-CUS: T-cell clonality of uncertain significance

Table 3: Spectrum of autoimmune disease

Autoimmune disease**	T-CUS/AID (n=39)	LGL-L/AID* (n=44)	Total (n=83)	p-value
Autoimmune cytopenias[†], n (%)	7 (18%)	11 (25%)	18 (22%)	0.43
PRCA	0 (0%)	3 (7%)	3 (4%)	0.09
ITP	4 (10%)	6 (14%)	10 (12%)	0.74
AIN [¶]	0 (0%)	2 (5%)	2 (2%)	0.17
Connective tissue diseases[†], n (%)	5 (13%)	9 (20%)	14 (17%)	0.35
SS	2 (5%)	4 (9%)	6 (7%)	0.49
SLE	2 (5%)	1 (2%)	3 (4%)	0.6
APS, n (%)	3 (8%)	1 (2%)	4 (5%)	0.34
Vasculitis[†], n (%)	8 (20%)	3 (7%)	11 (13%)	0.06
Small vessels [‡]	5 (13%)	1 (2%)	6 (7%)	0.06
Large vessels	3 (8%)	2 (5%)	5 (6%)	0.66
Granulomatous diseases, n (%)	11 (28%)	2 (5%)	13 (16%)	<0.01
Rheumatoid arthritis, n (%)	0 (0%)	18 (41%)	18 (22%)	<0.0001
Autoinflammatory diseases[†], n (%)	3 (8%)	3 (7%)	6 (7%)	1
AS, IBD spectrum[†], n (%)	2 (5%)	4 (9%)	6 (7%)	0.68
PAH, n (%)	2 (5%)	2 (5%)	4 (5%)	1
PID, n (%)	4 (10%)	0 (0%)	4 (5%)	<0.05
HES[†], n (%)	6 (15%)	2 (5%)	8 (10%)	0.14
Endocrinopathies, n (%)	4 (10%)	3 (7%)	7 (8%)	0.7
Other diseases^{†#}, n (%)	8 (20%)	3 (7%)	11 (13%)	0.06

*Including four patients considered as grey zone (low-count LGL) cases

**Different AID may coexist in a same patient. p-value <0.05

‡ Cryoglobulinemic vasculitis, ANCA-related vasculitis and cutaneous vasculitis

† Within subcategories, diagnoses may overlap within the same patient; however, each patient was counted only once in the corresponding main category

¶ AIN was defined solely on the detection of anti-neutrophil antibodies

Alveolar hemorrhage, interstitial lung disease, Primary biliary cirrhosis, autoimmune hepatitis, recurring pleuropericarditis, idiopathic cirrhosis, pachymeningitis, retroperitoneal fibrosis, Tubulointerstitial nephritis and uveitis syndrome, vitiligo, unclear diagnosis, Vogt-Koyanagi-Harada

AIN: Autoimmune neutropenia, APS: Antiphospholipid syndrome, AS: ankylosing spondylitis, HES: hypereosinophilic syndrome, IBD: inflammatory bowel disease, LGL-L: large granular lymphocyte leukemia, PAH: pulmonary artery hypertension, PID: primary immune deficiency, PRCA: Pure red cell aplasia, T-CUS: T-cell clonality of uncertain significance, SLE: systemic lupus erythematosus, SS: Sjögren syndrome

Table 4: Treatments and outcomes

	T-CUS (n=39)	LGL-L* (n=44)	Total (n=83)	p-value
Patients treated, n (%)	28 (72%)	37 (84%)	65 (78%)	0.17
Indication for treatment[‡]				
AID only, n (%)	28 (100%)	23 (62%)	51 (78%)	<0.001
Neutropenia (alone or combined indication) [†] , n (%)	0 (0%)	14 (38%)	14 (21%)	<0.001
Glucocorticoids[‡], n (%)	28 (100%)	30 (81%)	58 (89%)	<0.05
Immunosuppressants[‡], n (%)	22 (79%)	34 (92%)	56 (86%)	0.12
T-cell targeted therapies^{¶‡}, n (%)	19 (68%)	30 (81%)	49 (75%)	0.22
Number of therapeutic lines, median (IQR)	2 (0-3)	2 (1-4)	2 (1-3)	0.14
Death, n (%)	4 (10%)	3 (7%)	7 (8%)	0.7

*Including four patients considered as grey zone (low-count LGL) cases

† Neutropenia as the indication for treatment, either alone or in combination with AID-related indications.

‡ Percentages calculated among treated patients.

¶ T-cell-targeted therapies included methotrexate, cyclosporine, cyclophosphamide, azathioprine, and mycophenolate mofetil

IQR: Interquartile range, LGL-L: large granular lymphocyte leukemia, T-CUS: T-cell clonality of uncertain significance

Figure 1: Flow chart of the study

AID: Autoimmune disease, LGL-L: large granular lymphocyte leukemia, T-CUS: T-cell clonality of uncertain significance

Figure 2: Mutational landscape

* $p < 0.05$; ** $p < 0.01$

LGL-L: large granular lymphocyte leukemia, T-CUS: T-cell clonality of uncertain significance

147 patients screened
Across the six participating centers and through national call of observations

Not included : 54 patients

- Absence of auto-immune/inflammatory disease (AID)

96 patients considered for analysis

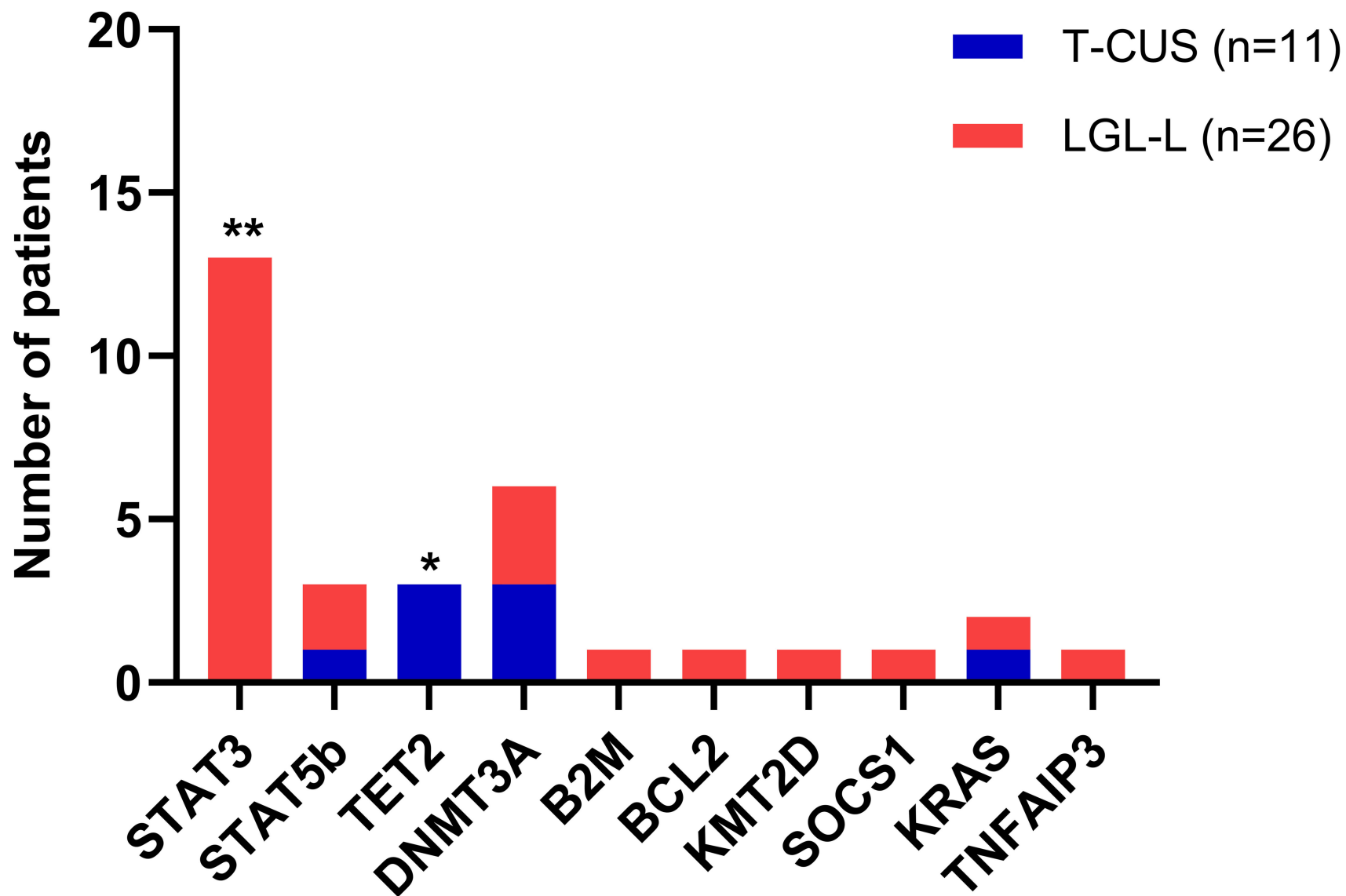
Excluded : 13 patients

- Absence of TCR rearrangement
- T-cell clonality not controlled within 3 months
- NK-cell clonal expansion
- T-cell lymphoma or acute leukemia

83 patients included

T-CUS + AID:
39 patients

T-LGL leukemia + AID:
44 patients



Supplementary appendix

T-cell clonal expansion associated with autoimmune and inflammatory diseases

This Supplementary Appendix provides additional tables and figures supporting the analyses presented in the main article.

Supplementary Tables

Table S1: Detailed distribution of autoimmune disease observed in the cohort

Table S2: Other hematological malignancies and premalignant conditions

Table S3: Treatment outcomes with T-cell–targeted therapy and other immunosuppressors in the cohort

Supplementary Figures

Figure S1: Kaplan-Meier for event-free survival

Figure S2: Immunophenotypic characteristic according to autoimmune disease

Figure S3: Spectrum of autoimmune disease

List of Abbreviations

Supplementary Tables

Table S1: Detailed distribution of autoimmune disease observed in the cohort

Autoimmune disease**	TCUS (n=39)	LGL-L* (n=44)	Total (n=83)	p-value
Autoimmune cytopenias†, n (%)	7 (18%)	11 (25%)	18 (22%)	0.43
PRCA	0 (0%)	3 (7%)	3 (4%)	0.09
AIN†¶	0 (0%)	2 (5%)	2 (2%)	
AIHA	3 (8%)	3 (7%)	6 (7%)	1
ITP	4 (10%)	6 (14%)	10 (12%)	0.74
Evans syndrome	0 (0%)	3 (7%)	3 (4%)	0.24
Connective tissue diseases†, n (%)	5 (13%)	9 (20%)	14 (17%)	0.35
SLE	2 (5%)	1 (2%)	3 (4%)	0.6
SS	2 (5%)	4 (9%)	6 (7%)	0.49
SSc	1 (3%)	2 (5%)	3 (4%)	1
Mixed connective tissue	1 (3%)	0 (0%)	1 (1%)	
Dermatomyositis	0 (0%)	2 (5%)	2 (2%)	
Antisynthetase syndrome	0 (0%)	1 (2%)	1 (1%)	
APS, n (%)	3 (8%)	1 (2%)	4 (5%)	0.34
Vasculitis†, n (%)	8 (18%)	3 (7%)	11 (13%)	0.06
ANCA related	4 (10%)	0 (0%)	4 (5%)	<0.05
Cutaneous	1 (3%)	0 (0%)	1 (1%)	
Cryoglobulinemic	0 (0%)	1 (2%)	1 (1%)	
Primary cerebral vasculitis	0 (0%)	1 (2%)	1 (1%)	
Giant cell arteritis with RPP	2 (5%)	1 (2%)	3 (4%)	0.6
Giant cell arteritis without RPP	1 (3%)	1 (2%)	2 (2%)	
Granulomatous diseases, n (%)	11 (28%)	2 (5%)	13 (16%)	<0.01
Sarcoidosis	6 (15%)	2 (4%)	8 (10%)	0.09
Other granulomatosis	2 (5%)	0 (0%)	2 (2%)	
EGPA	2 (5%)	0 (0%)	2 (2%)	
GPA	1 (3%)	0 (0%)	1 (1%)	
Rheumatoid arthritis, n (%)	0 (0%)	18 (41%)	18 (22%)	<0.0001
Autoinflammatory diseases†, n (%)	3 (8%)	3 (7%)	6 (7%)	1
Behcet like	1 (3%)	1 (2%)	2 (2%)	
VEXAS syndrome	0 (0%)	1 (2%)	1 (1%)	

Still disease	1 (3%)	1 (2%)	2 (2%)	
AS, IBD spectrum†, n (%)	2 (5%)	4 (9%)	6 (7%)	0.68
AS	0 (0%)	3 (7%)	3 (4%)	0.24
IBD	2 (5%)	2 (5%)	4 (5%)	1
PAH, n (%)	2 (5%)	2 (5%)	4 (5%)	1
PID, n (%)	4 (10%)	0 (0%)	4 (5%)	<0.05
CVID	2 (5%)	0 (0%)	2 (2%)	
ALPS	1 (3%)	0 (0%)	1 (1%)	
HES†, n (%)	6 (15%)	2 (5%)	8 (10%)	0.14
Digestive impairment	1 (3%)	1 (2%)	2 (2%)	
Cutaneous impairment	3 (8%)	1 (2%)	4 (5%)	
Pulmonary impairment	1 (3%)	1 (2%)	2 (2%)	
Endocrinopathies, n (%)	4 (10%)	3 (7%)	7 (8%)	0.7
T1D	0 (0%)	1 (2%)	1 (1%)	
Thyroiditis	4 (10%)	2 (5%)	6 (7%)	0.41
Other diseases†, n (%)	8 (20%)	3 (7%)	11 (13%)	0.06
Retroperitoneal fibrosis	2 (5%)	0 (0%)	2 (2%)	
Vitiligo	1 (3%)	0 (0%)	1 (1%)	
Primary biliary cirrhosis	1 (3%)	0 (0%)	1 (1%)	
Autoimmune hepatitis	0 (0%)	1 (2%)	1 (1%)	
Recurring pleuropericarditis	0 (0%)	1 (2%)	1 (1%)	
Idiopathic cirrhosis	1 (3%)	0 (0%)	1 (1%)	
TINU-syndrome	1 (3%)	0 (0%)	1 (1%)	
ILD	1 (3%)	1 (2%)	2 (2%)	
Alveolar hemorrhage	1 (3%)	0 (0%)	1 (1%)	
Pachymeningitis	1 (3%)	0 (0%)	1 (1%)	
Unclear diagnosis	3 (8%)	2 (5%)	5 (6%)	

* Including four patients considered as grey zone (low-count LGL) cases

** Patients may be counted in several disease category

† Within subcategories, diagnoses may overlap within the same patient; however, each patient was counted only once in the corresponding main category

¶ AIN was considered only on the presence of antibody against neutrophils

AHIA: Autoimmune haemolytic anemia, ALPS: Autoimmune lymphoproliferative syndrome, ANCA: anti-neutrophil cytoplasmic antibody, APS: Antiphospholipid syndrome, AS: ankylosing spondylitis, CVID: Common variable immune deficiency, HES: hypereosinophilic syndrome, IBD: inflammatory bowel disease, ILD: Interstitial lung disease, ITP: Immune thrombocytopenia, LGL-L: large granular lymphocyte leukemia, PAH: pulmonary artery hypertension, PID: primary immune deficiency, PRCA: Pure red cell aplasia, RPP: Rhizomelic pseudo-polyarthritides, SLE: systemic lupus erythematosus, SS: Sjögren's syndrome, SSc: Systemic sclerosis, T-CUS: T-cell clonality of uncertain significance, T1D: type1diabetes, TINU: Tubulointerstitial nephritis and uveitis, VKH: Vogt-Koyanagi-Harada

Table S2: Other hematological malignancies and premalignant conditions

	T-CUS (n=39)	LGL-L* (n=44)	Total (n=83)	p-value
Other hematological comorbidities	10 (26%)	10 (23%)	20 (24%)	0.8
Lymphoid				
MBL, n (%)	0 (0%)	2 (5%)	2 (2%)	0.24
MGUS, n (%)	1 (3%)	2 (5%)	3 (4%)	1
DLBCL, n (%)	5 (13%)	1 (2%)	6 (7%)	0.09
HL, n (%)	1 (3%)	0 (0%)	1 (1%)	0.47
MALT lymphoma, n (%)	1 (3%)	3 (7%)	4 (5%)	0.62
MZL, n (%)	1 (3%)	0 (0%)	1 (1%)	0.47
Myeloid				
MDS, n (%)	1 (3%)	1 (2%)	2 (2%)	1
CMML, n (%)	0 (0%)	1 (2%)	1 (1%)	1

* Including four patients considered as grey zone (low-count LGL) cases

CMML: chronic myelomonocytic leukemia, DLBCL: diffuse large B-cell lymphoma, LGL-L: large granular lymphocyte leukemia, MZL: marginal zone lymphoma, MALT: mucosa-associated lymphoid tissue, MBL: monoclonal B -cell lymphocytosis, MGUS: monoclonal gammopathy of uncertain significance, MDS: myelodysplastic syndrome, T-CUS: T-cell clonality of uncertain significance

Table S3: First line treatment outcomes with T-cell–targeted therapy and other immunosuppressants

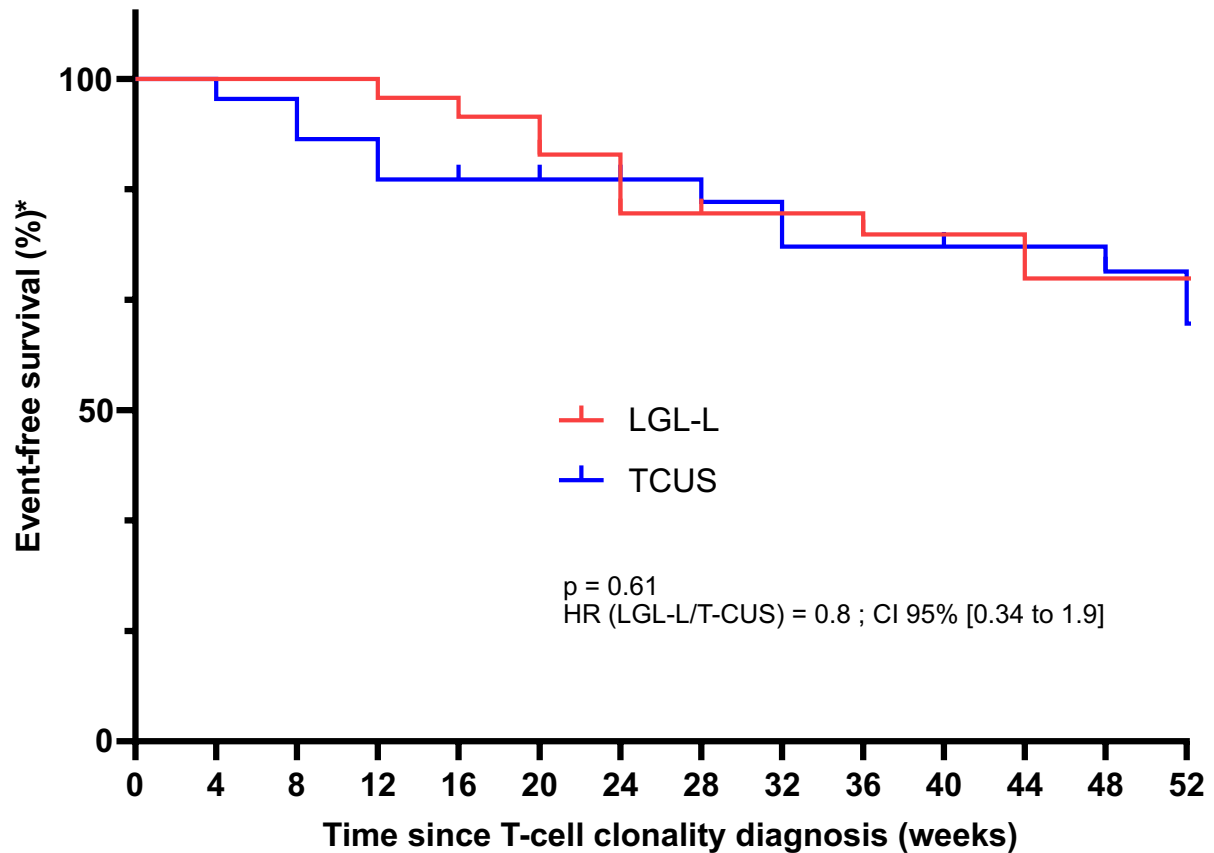
First-line therapy	Target T-cell therapies (n=38)			Other immunosuppressants (n=18)		
	T-CUS (n=13)	LGL-L (n=25)	p-value	T-CUS (n=9)	LGL-L (n=9)	p-value
Complete response	8 (61%)	12 (48%)	0.51	3 (33%)	4 (44%)	1
Partial response	0 (0%)	1 (4%)	1	1 (11%)	0 (0%)	1
Overall response	8 (61%)	13 (52%)	0.74	4 (44%)	4 (44%)	1
Treatment failure*	5 (38%)	12 (48%)	0.73	5 (56%)	5 (56%)	1

*Relapse, lack of efficacy or toxicity

Percentages and statistical comparisons were calculated among patients treated with the corresponding immunosuppressive therapy.

LGL-L: large granular lymphocyte leukemia, T-CUS: T-cell clonality of uncertain significance

Supplementary Figures



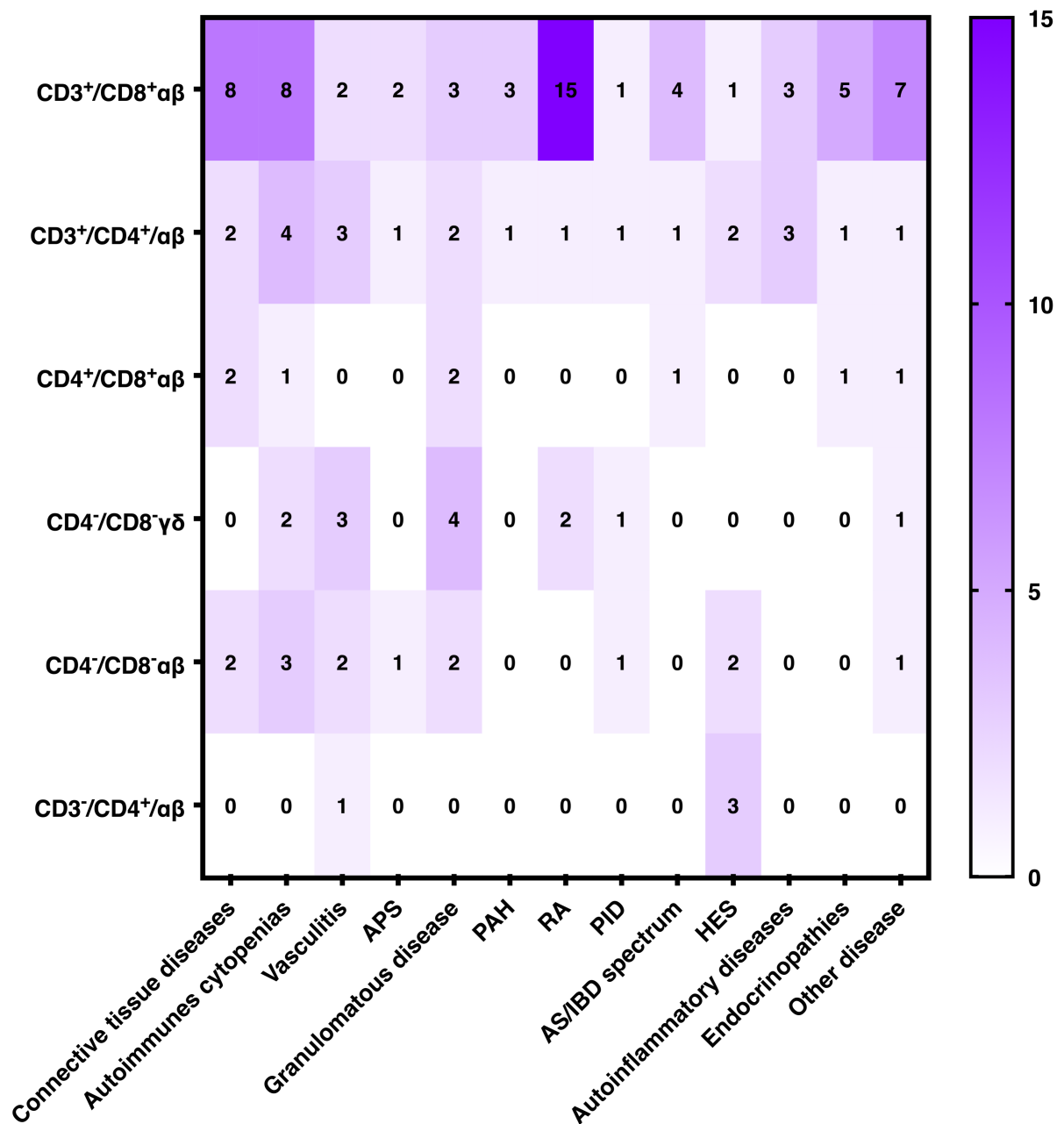
LGL-L	...	39 (0)	39 (0)	39 (0)	38 (0)	37 (2)	33 (4)	28 (5)	27 (5)	27 (6)	25 (6)	25 (6)	23 (6)	...
T-CUS	...	29 (0)	28 (0)	26 (0)	24 (1)	23 (1)	23 (1)	23 (1)	22 (1)	20 (1)	20 (3)	18 (3)	18 (4)	...
	0	4	8	12	16	20	24	28	32	36	40	44	48	52

*Relapse, next treatment or death

Event-free survival was assessed among treated patients only and was calculated from treatment initiation to relapse, initiation of a subsequent treatment, or death.

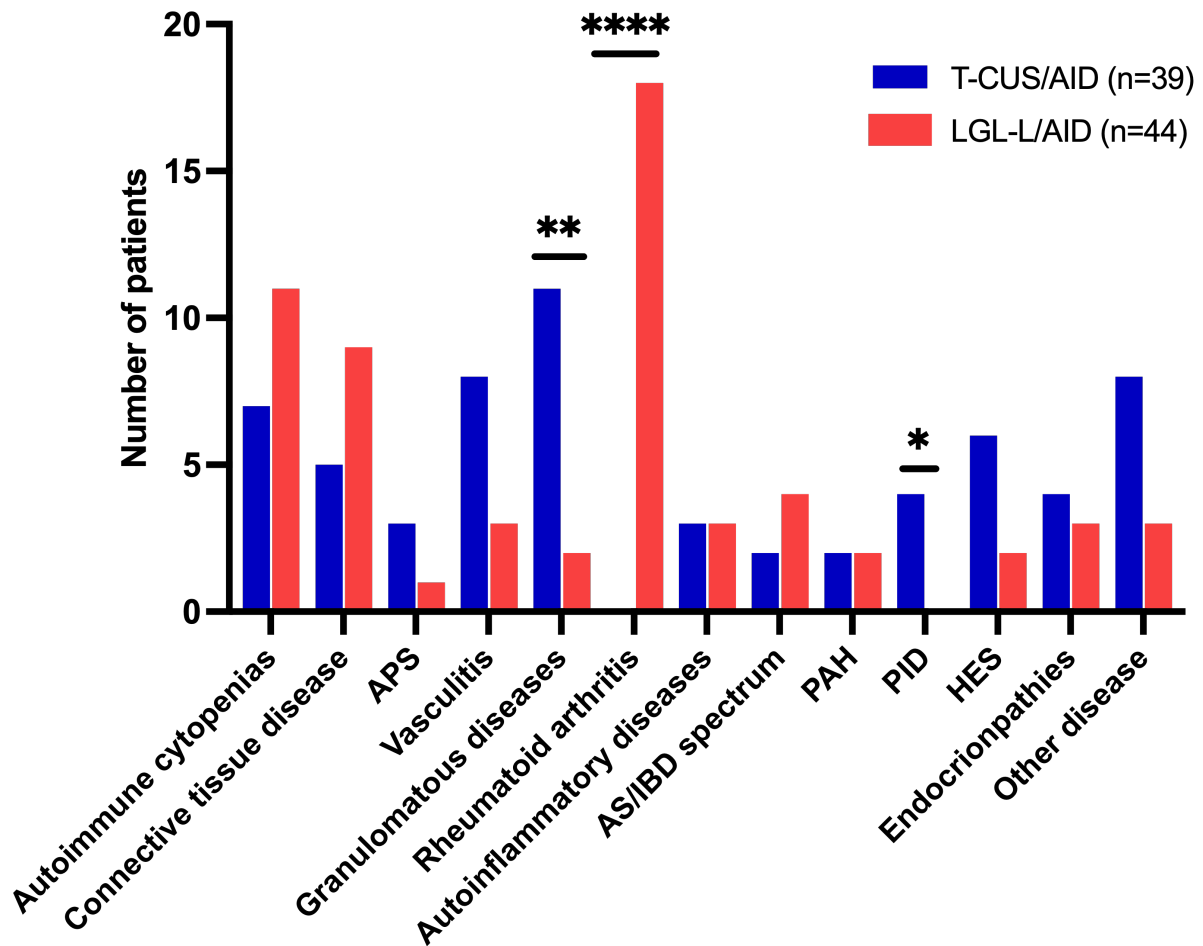
CI: Confidence interval, HR: Hazard ratio, LGL-L: large granular lymphocyte leukemia, T-CUS: T-cell clonality of uncertain significance

Figure S1: Kaplan-Meier for event-free survival



APS: Antiphospholipid syndrome, AS: ankylosing spondylitis, HES: hypereosinophilic syndrome, IBD: inflammatory bowel disease, PAH: pulmonary artery hypertension, PID: primary immune deficiency, RA: rheumatoid arthritis

Figure S2: Immunophenotypic characteristic according to autoimmune disease



APS: Antiphospholipid syndrome, AS: ankylosing spondylitis, HES: hypereosinophilic syndrome, IBD: inflammatory bowel disease, LGL-L: large granular lymphocyte leukemia, PAH: pulmonary artery hypertension, PID: Primary immune deficiency, T-CUS: T-cell clonality of uncertain significance

* $p<0.05$, ** $p<0.01$, **** $p<0.0001$

Figure S3: Spectrum of autoimmune disease

List of Abbreviations

AID	Autoimmune Disease
AHIA	Autoimmune Hemolytic Anemia
ALPS	Autoimmune lymphoproliferative syndrome
ANCA	Antineutrophil cytoplasmic antibody
APS	Antiphospholipid Syndrome
AS	Ankylosing spondylitis
CHIP	Clonal Hematopoiesis of Indeterminate Potential
CMML	Chronic myelomonocytic leukemia
DLBCL	Diffuse large B cell lymphoma
DNMT3A	DNA Methyltransferase 3 Alpha
HES	Hypereosinophilic Syndrome
HL	Hodgkin lymphoma
HR	Hazard ratio
IBD	Inflammatory Bowel Disease
IL	Interleukin
IQR	Interquartile range
ITP	Immune Thrombocytopenia
KMT2D	Lysine Methyltransferase 2D
LGL-L	Large Granular Lymphocyte leukemia
MALT	Mucosa-associated lymphoid tissue
MBL	Monoclonal B-cell lymphocytosis
MDS	Myelodysplastic syndrome
MGCS	Monoclonal gammopathy of clinical significance
MGUS	Monoclonal gammopathy of undetermined significance
MHC	Major histocompatibility complex
MZL	Marginal Zone lymphoma
NK	Natural Killer
PAH	Pulmonary artery hypertension
PID	Primary immune deficiency
SLE	Systemic Lupus Erythematosus
SS	Sjögren syndrome
SSc	Systemic sclerosis
RA	Rheumatoid Arthritis
STAT3	Signal Transducer and Activator of Transcription 3
STAT5B	Signal Transducer and Activator of Transcription 5B
T-CUS	T-cell Clone of Uncertain Significance
TCR	T-Cell Receptor
TET2	Tet Methylcytosine Dioxygenase 2