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Large granular lymphocytic laeukemia after solid organ and haematopoietic stem cell transplantation

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Summary:

T-cell large granular lymphocyte leukaemia (T-LGLL) is a chronic clonal lymphoproliferative disorder of cytotoxic T lymphocytes (CTL), which commonly occurs in older patients and is often associated with autoimmune diseases. Among 246 patients with T-LGLL seen at our institution over the last 10 years, we encountered 15 cases following solid organ or haematopoietic stem cell transplantation. Here, we studied the clinical characterization of these cases and compared them to de novo T-LGLL. This experience, represented a clear picture of the intricate nature of the disease manifestation and the complexities of several immune mechanisms triggering the clonal expansion.

Keywords

LGLL; solid organ transplantation; bone marrow transplantation

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Authorship Contributions

H. A. collected, analyzed and interpreted the clinical information and wrote the manuscript; R.Z.M participated to the study and edited the manuscript; J.D., A.K. collected clinical data; V.V. edited the manuscript and interpreted the data; B.K.H., H.E.C, A.E.L., D.J., B.T.H., A.N., N.S.M., R.S., M.K., M.A.S. provided patients, edited the manuscript and added important insights to the manuscript; J.P.M followed the patients, designed the study and wrote the manuscript.

Conflicts-of-Interests Disclosures

The authors have nothing to disclose

T-cell large granular lymphocytic leukaemia (T-LGLL) is a chronic clonal lymphoproliferative syndrome of cytotoxic T lymphocytes (CTL). T-LGLL occurs most commonly in older patients and is often associated with autoimmune diseases such as rheumatoid arthritis (RA), B cell dyscrasias, non-hematologic cancers and immunodeficiency (*e.g.*, hypogammaglobulinemia). While there is a great deal of overlap with reactive (physiologic) CTL responses, some cases are autonomous due to the acquisition of *STAT3* mutations ($STAT3^{MT}$) (Andersson et al, 2013). Similarly, the clinical spectrum of manifestations ranges from self-limited polyclonal expansion to oligo/monoclonal lymphocytosis or even to an overt LGL leukaemia (LGLL) with cytopenia as a paraneoplastic clinical presentation. The resemblance of LGLL manifestations to reactive immune processes leads to frequent diagnostic dilemmas; LGLL looks like and behaves like CTL during viral infections, for instance during Epstein Barr virus (EBV) associated infectious mononucleosis.

Exuberant CTL responses (presumed origin of LGLL) can be envisioned in autoimmune processes, strong immune reactions due to alloantigen stimulation in graft rejection or graft-*vs*-host disease (GvHD) or over-compensatory CTL reactions to infectious agents in the setting of humoral immunodeficiency [*e.g.*, hypogammaglobulinemia, common variable immunodeficiency (CVID)] (Viny et al, 2008). Previously, we and others described clonally skewed CTL responses and oligoclonal immunodominant T cell clonotypes following allogeneic haematopoietic stem cell transplantation (HSCT) (O'Keefe et al, 2004 & O'Keefe et al, 2007 & Li et al, 2015). Such skewed CTL responses, are reminiscent of T-LGLL we repeatedly encountered in allotransplant recipients. Additionally, our meta-analysis of case reports and series (1994-2014) has identified 62 cases (solid organ transplantation: SOT, n=22; HSCT–associated T-LGL/LGLL, n=40) seen in 10 different institutions (Table S1). However, early historical reports while clinically insightful, were not all uniformly diagnosed with some of the cases likely corresponding to oligoclonality skewed reactive CTL responses rather than real T-LGLL. For instance, in one series, diagnostic confirmation was available in only 5/13 cases (Nann-Rutti et al, 2012). It is likely that only a fraction of the reported cases represented a true "WHO-defined T-LGLL" manifestation (Swerdlow et al, 2016). In our cohort, all cases were stringently and uniformly diagnosed when 3 out of 4 following criteria were fulfilled, including: 1) LGL count >500/μL in blood for more than 6 months; 2) presence of abnormal CTLs expressing CD3, CD8 and CD57 by flow cytometry; 3) preferential usage of a TCR Vβ family by flow cytometry; 4) TCR gene rearrangement by PCR. Moreover, targeted deep sequencing for $STAT3^{MT}$ (Koskela et al, 2012; Sanikommu et al, 2018) was performed as well as bone marrow biopsies to exclude other conditions. Here, we report an analysis of 15 cases of overt T-LGLL following SOT (n=8) and HSCT (n=7; Table 1). Overall, these cases constituted 6% of a total of 246 adult patients with T-LGLL seen in our clinic over the last 10 years. While this series is not the first report of the *post*-transplantation T-LGLL, it is the first to aim to comprehensively study "WHO-defined T-LGLL" in both SOT and HSCT simultaneously and to compare them to a control group of *de novo* T-LGLL (cases with no prior history of SOT or HSCT; n=231).

In our cohort, diagnosis was made 0.2-27 years *post*-transplantation (median: 4 years) suggesting a diverse etiology of T-LGLL. Signs of rejection were observed in 20% (n=3/15)

and GvHD in 13% (n=2/15) of the patients (Table 1). Interestingly, T-LGLL evolved in 10 patients (67%; 10/15) despite concurrent immunosuppressive therapy (acquired immunodeficiency) including cyclosporine (n=5), tacrolimus (n=4), mycophenolate mofetil (n=5), cyclophosphamide (n=1), anti-thymocyte globulin (n=1), and corticosteroids (n=6). Pre-existing immunodeficiency including hypogammaglobulinemia, was present in 3 cases with 2 patients having diagnosis of CVID. *Post*-transplantation, 27% of cases presented with neutropenia (absolute neutrophil count <1.5 $x10^9$/L; n=4), 33% with thrombocytopenia (platelet count <150 $x10^9$/L; n=5) and 25% with anemia (hemoglobin <10 g/dL; n=3) (Table S2). Lymphadenopathy and splenomegaly were seen in 13% (n=2) and 33% (n=5) of the patients, respectively. Other associated conditions observed were monoclonal gammopathy of undetermined significance (MGUS, 20%; n=3) and RA (7%; n=1). At the time of T-LGLL diagnosis, relative lymphocytosis (15-91%), T lymphocytosis (49-99%) and elevated absolute LGL counts (>500 /μL; in 93% of cases) were also seen. TCR Vβ analysis identified clonal expansion of ≥1 of the Vβ proteins in 60% (n=9) of the cases; the remaining 40% (n=6) of the cases showed either a clonal process involving a Vβ protein not tested in the panel (20%; n=3) or no obvious expansion (20%; n=3). TCR gene re-arrangements were present in all tested patients (100%; 14/14). Conventional cytogenetic showed 89% normal karyotype (n=11, tested individuals 13/15). Somatic $STAT3^{MT}$ were identified in 15% of patients (n=2, sequenced individuals 13/15). Bone marrow evaluations in all the patients ruled out other differential etiologies for cytopenia including: myelodysplastic syndromes, aplastic anemia, pure red cell aplasia or others. All patients were tested for EBV and CMV DNA by PCR in addition to serologies of their specific IgM and IgG antibodies; 60% of cases (n=9) were seropositive for EBV when tested at different time points after transplant. Similarly, 53% (n=8) were seropositive for CMV, of which, 5 were positive *post*-transplantation only and 3 *pre*-/*post*-transplantation. In terms of treatment, indications included neutropenia or mixed cytopenia. Therapies, initial and overall response rates among these patients were summarized in Table S3.

As compared to *de novo* T-LGLL, *post*-transplantation T-LGLL patients were significantly younger (median age: 55 *vs*. 65 years; P=0.0002; Table 2), consistent with a younger age of patients undergoing transplantation. *Post*-transplantation T-LGLL was also characterized by significantly higher absolute LGL count (median: 4.5 *vs*. 8.5 k/μ, P=0.0005), reduced neutropenia but similar incidence of thrombocytopenia (27 *vs*. 43%, P=0.3 and 33 *vs*. 35%, P=1, respectively) and significantly lower odds of anemia (20% *vs*. 55%; P=0.01) likely due to a higher specialized medical care after transplantation, while *de novo* cases may represent a more symptomatic tip of the iceberg in a clinical continuum of T-LGLL. To that end, a more objective marker (*e.g.*, $STAT3^{MT}$ and cytogenetic abnormalities) did not differ between the groups suggesting a similar pathophysiologic mechanism.

T-LGLL likely arises in the context of a polyclonal CTL response, which upon chronic stimulation undergoes conversion to more oligo- and then monoclonal rearrangements. Several mechanisms of clonal expansion *post*-transplantation may be responsible, including active viral infections, latent oncogenic viral reactivation, graft allo-antigenic stimulation or reactivation of pre-existing autoimmune process (Fig.1). In general, albeit oligoclonal skewing has been described after transplantation (Gorochov et al, 1994; Mohty et al, 2002; Sabnani et al, 2006; Qiu et al, 2017), the vast majority of patients with this

complication are not known to develop T-LGLL. Theoretically, T-LGLL may originate from *pre*-transplantation autoimmunity of the donor in HSCT or recipient in SOT, which has been augmented by a heightened level of immune responsiveness due to allo-stimulation. While autoimmune conditions were present in 50% of SOT recipient (n=4/8, including RA, systemic lupus erythematosus), this type of past medical history is not available for HSCT graft donors. Previously, we have described that inherited or acquired hypogammaglobulinemia is associated with T-LGLL (Viny et al, 2008). Indeed, some of our patients had low immunoglobulin levels. However, hypogammaglobulinemia may be a mere marker of immunodeficiency in transplantation recipients due to immunosuppression, GvHD-associated immunosuppression or chronic disease. Overt EBV (*post*-transplant lymphoproliferative disorder) and CMV reactivation have been diagnosed in only 27% (4/15) of the patients, but similar undiagnosed infection may be present in an immunosuppressed host. According to this theory, inability to mount antibody or cellular response could result in persistent, unresolved infection and thus chronic CTL stimulation. Such an immunosuppressive state has been described in typical T-LGLL in the form of hypogammaglobulinemia, prior history of cancers, lymphoma, or co-existence with B-cell dyscrasias and may also be present following autologous HSCT. Others have encountered T-LGLL in auto-HSCT (8 cases in 3 studies), and in our series in 3 patients. However, it is difficult to establish a causative relationship in this cohort given that these patients also had history of lymphoma (diffuse large B-cell, mantle cell lymphoma, chronic lymphocytic leukaemia/small lymphocytic leukaemia).

In sum, our report highlights the intricate nature of T-LGLL evolution following SOT and HSCT and points out the complexities of several postulated mechanisms. While the origin of LGLL in these patients is difficult to identify, it would be interesting to find the risk of transmission through the donated transplantation graft versus evolution from the recipient cells itself following the procedure. Our cohort does not have sufficient information from the donor available, making this difficult to answer. Undoubtedly, a comprehensive review of the medical history of the patients and scrutiny of their *pre vs. post*-transplantation baseline, clinical and molecular characteristics is warranted to better understand this phenomenon. Routine long-term blood analysis for LGL should be considered in immunosuppressed/*post*-transplantation patients, regardless of viral infection, to monitor T-LGLL evolution.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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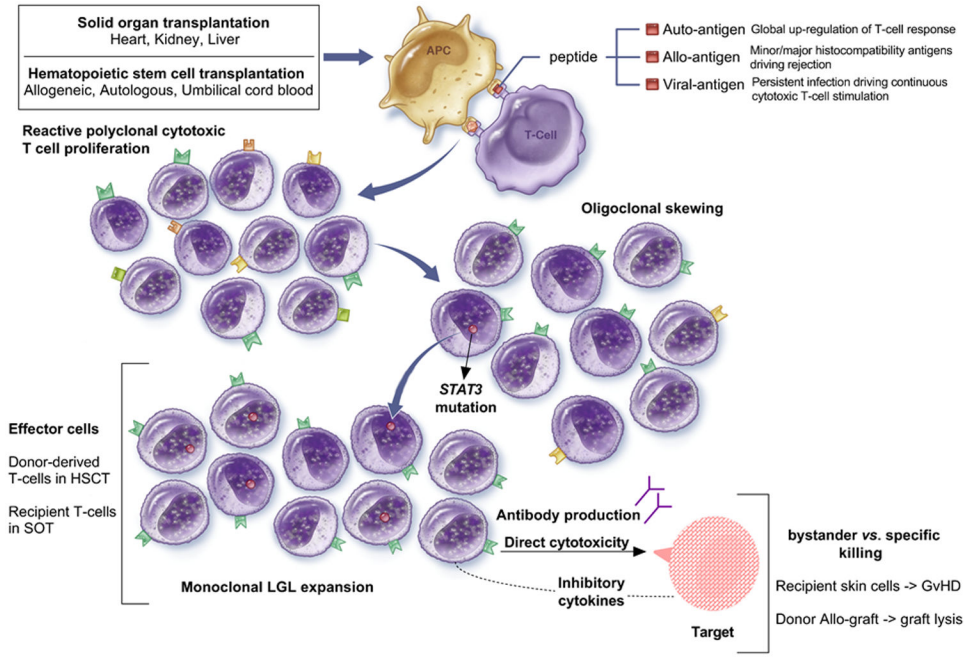

Figure 1. Development of large granular lymphocytic leukaemia after transplantation.

Several mechanisms have been postulated to explain T-cell large granular lymphocytes clonal proliferation after solid organ and haematopoietic stem cell transplantation, as summarized. (Abbreviations: APC, antigen presenting cell; HSCT, haematopoietic stem cell transplantation; SOT, solid organ transplantation; LGL, LGLL, large granular lymphocytes; GvHD, graft versus host disease).

Table 1.

Type of transplantation and individual characteristics of *post*-transplantation T-LGLL patients

Case	Age*/Gender	Antecedent diagnosis	Type of transplant	Immunosuppressive therapy	Organ rejection	T-cell chimerism	GvHD	Time since transplant (y)
1	53/M	DLBCL	autologous SCT	−	NA		−	7
2	59/M	ESRD/cardiomyopathy	kidney/heart	CsA, MMF	+	GF	−	8/25
3	38/M	cardiomyopathy	heart	Gc	−	NA*	−	4
4	31/F	ESRD	kidney	ATG, Tac, Gc, MMF	−	NA*	−	3.6
5	16/M	aplastic anemia	allogeneic SCT	CsA, Gc	+	GF	−	0.3
6	55/M	CLL/SLL	autologous SCT	−	NA		−	2
7	57/M	HCV cirrhosis	liver	CsA, Gc	−	NA*	−	26
8	58/M	mantle cell lymphoma	autologous SCT	−	NA		−	0.2
9	43/M	lupus nephritis	kidney	Tac, Gc, CP	+	GF	−	13
10	60/F	PSC	liver	Tac	−	NA*	−	13
11	57/F	ESRD	kidney	Tac, MMF, Gc	−	NA*	−	7
12	65/M	HBV cirrhosis	liver	−	−	NA*	−	27
13	39/F	CML	UCBT	−	−	C	−	0.5
14	57/F	ALL	allogeneic SCT	CsA, MMF	−	C	+	4
15	36/F	ALL	allogeneic SCT	CsA, MMF	−	C	+	3.7

*At time of T-LGLL diagnosis

Abbreviations: M, male; F, female; DLBCL, diffuse large B-cell lymphoma; ESRD, end-stage renal disease, CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic leukaemia; HCV, hepatitis C virus; PSC, primary sclerosing cholangitis; HBV, hepatitis B virus; CML, chronic myelogenous leukaemia; ALL, acute lymphoblastic leukaemia; SCT, stem cell transplant; UCBT, umbilical cord blood transplant; CsA, cyclosporine A; MMF, mycophenolate mofetil; Gc, glucocorticoids; ATG, anti-thymocyte globulin; Tac, tacrolimus; CP, cyclophosphamide; GvHD, graft versus host disease; y, years; +, present; −, absent; NA, not applicable; NA*, not available; GF, primary graft failure, C, complete/full donor chimerism achieved.

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Table 2.

Baseline and clinical features of *de novo vs. post*-transplantation T- LGLL cases

Variables	*de novo* T-LGLL	PT T-LGLL	*P*-value
Total (n)	231	15	
Age, median (range) in years	65 (18-89)	55 (16-65)	**0.0002** [A]
≥ 60 y, n(%)	159 (69)	2 (13)	**<0.0001** [B]
Gender			
M/F	53/47	60/40	0.6 [B]
Conventional cytogenetic [†]			
Abnormal, n(%)	8 (3)	2 (15)	0.07 [B]
LGL count, median (range) in k/μL	1.3 (0.01-970)	4.5 (0.1-12.4)	**0.0005** [A]
TCR-R [†], n(%)	140 (96)	14 (100)	1 [B]
***STAT3*^{MT}** [†], n(%)	87 (39)	2 (15)	0.1 [B]
Splenomegaly	60 (26)	5 (33)	0.5 [B]
Hematological features [*]			
Neutropenia, n(%)	99 (43)	4 (27)	0.3 [B]
Anemia, n(%)	127 (55)	3 (20)	**0.01** [B]
Thrombocytopenia, n(%)	80 (35)	5 (33)	1 [B]

[†] Some data were unable to assess

[*] Neutropenia, absolute neutrophil count <1.5 x 10^9/L; Anemia, hemoglobin <10 g/dL; Thrombocytopenia, platelet count <150 x 10^9/L.

Abbreviations: T-LGLL, T-cell large granular lymphocytic leukaemia; PT T-LGLL, *post*-transplant T-cell large granular lymphocytic leukaemia; TCR-R, T-cell receptor gene rearrangement; *STAT3*^{MT}, *STAT3* mutant; M, male; F, female; y, years; n, number.

[A] Wilcoxon test, 2-sided

[B] Fisher's exact test

Significantly different parameters are in bold text.