Published in final edited form as:
Exp Hematol. 2008 September ; 36(9): 1078–1083. doi:10.1016/j.exphem.2008.04.005.

OUTCOMES OF SPLENECTOMY IN T CELL LARGE GRANULAR LYMPHOCYTE LEUKEMIA WITH SPLENOMEGALY AND CYTOPENIAS

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Abstract

Objective—T cell large granular lymphocyte leukemia (T-LGL) is a chronic clonal lymphoproliferation of cytotoxic T cells (CTL) often complicated by cytopenias. Because the outcomes of splenectomy in patients with T-LGL have been only sporadically reported we objectively assessed the outcomes of splenectomy.

Patients and Methods—When a cohort of 56 T-LGL patients was analyzed, patients with splenomegaly (n=34) and had higher frequency of bi- and pancytopenia than patients with no splenomegaly (70% vs. 27%; p=.001). We identified 15 patients who, in their clinical course, underwent splenectomy and studied their hematological and clinical outcomes.

Results—Indications for splenectomy included symptomatic splenomegaly and/or severe refractory cytopenias. Median spleen weight was 1300g, consistent with the diagnosis of splenomegaly; TCR-γ rearrangement and typical T-LGL were detected by immunophenotype in all specimens. There was no surgery-related mortality, with the median follow up and survival of 719 and 498 days, respectively. Two patients died due to causes possibly related to the splenectomized state and/or primary disease. All patients showed lineage-specific hematologic response and achieved transfusion independence; however, precise molecular analysis of TCR and Vβ flow cytometry showed persistence of the LGL clones.

Conclusion—We conclude that splenectomy constitutes a viable and safe therapeutic option for patients with T-LGL, splenomegaly and refractory cytopenias.

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Keywords

LGL; Splenectomy; CTL

INTRODUCTION

T cell large granular lymphocytic leukemia (T-LGL) is a chronic clonal lymphoproliferation of cytotoxic T lymphocytes (CTL) often associated with immune cytopenias[1,2]. Clinically, T-LGL overlaps with less polarized clonal expansions of CTL and polyclonal reactive processes occurring in the context of viral infections and autoimmune diseases[3,4]. In a significant proportion of patients T-LGL may be asymptomatic. Similarly, benign clonal expansions can be encountered in apparently healthy elderly individuals, a condition often referred to as monoclonal (T cell) clonopathy of unclear significance (MCUS, TCUS) [3,5,6]. The proliferation of CTL is not totally autonomous and may be a reflection of an exaggerated immune response possibly sustained by a persistent antigenic drive[3]. Alternative pathogenic mechanisms may include clonal acquisition of resistance in the context of polyclonal responses.

Diagnostic criteria for T-LGL include the presence of characteristic LGL on blood smear although the absolute LGL count has not been consistently set (either >.400 or >2000/uL of blood), evidence for flow cytometric population of abnormal CD3+,CD16+,CD28−,CD57+. CD8+ T cell population, and clonal T cell receptor (TCR)-γ rearrangement studies [2,7–10]. More than 1/3 of these patients present clinically with cytopenias, recurrent bacterial infections, and/or splenomegaly. Most common hematologic complications, lineage-restricted cytopenias, may be either a result of direct clone–mediated specific cytotoxicity directed against corresponding committed progenitors (erythroid or myeloid precursors in red cell aplasia or neutropenia, respectively) or due to cytokine-mediated proapoptotic effects [11,12]. Some patients may present also with hemolytic anemia. Moreover, cytopenias seen in T-LGL may also be a result of splenic sequestration.

Historically, splenectomy in T-LGL has been sporadically reported and improvement of counts has been reported following procedure[13]. Improvement of immune-mediated cytopenias has been reported following removal of an enlarged spleen [14,15]. Splenectomy can be effective also in immune thrombocytopenic purpura[16,17]. Its potential utility has also been demonstrated in various hematologic malignancies[18–21]. In Felty's syndrome (FS), a condition closely associated with T-LGL, splenectomy was an important component of treatment before the advent of its modern management[22]. Among 118 cases reported of FS treated by surgical splenectomy, immediate hematological resolution of neutropenia was reported in 100% of the patients. However, the response was not persistent, with 20% of patients relapsing within first 6 months [23]. Clinically, splenectomy is beneficial in relieving the gastrointestinal related symptoms of fullness, nausea, early satiety and pain related to splenomegaly.

To objectively assess the outcomes of splenectomy in patients with T-LGL we retrospectively analyzed a cohort of patients with T-LGL who underwent splenectomy for various clinical indications.

MATERIALS AND METHODS

Patients

Informed consent for the study of the patients' records and for the blood sample collection for the laboratory studies was obtained from the Institutional Review Board of the Cleveland

Clinic Foundation according to the established procedures. For the purpose of this study, we used modified diagnostic criteria as previously reported[7,24,25]. Diagnostic criteria included 1) presence of T cell receptor (TCR) γ-chain rearrangement, 2) detection of an expanded discrete cell population characterized by expression of CD3, CD8, CD16 and CD57 markers, 3) morphologic detection of LGL on blood smear (>.400/μL of blood) and/or 4) restricted usage of TCR variable chain β (Vβ) within T cell repertoire[3]. We analyzed samples from a total of 56 patients diagnosed with T-LGL leukemia between 2002 to 2007 (Table 1). Splenomegaly was identified by palpation or clinical suspicion and confirmed by ultrasound or CT scan. We identified 15 patients with T-LGL who, in their clinical course, underwent elective splenectomy (Table 2). Median follow up was 719 days. No patients were lost to follow up. All splenectomized patients received pneumococcal, meningococcal and haemophilus influenzae vaccination before surgery. Patients underwent either open (5/15) or laparoscopic splenectomy (10/15) depending on surgical conditions such as size of the spleen and prior surgical history.

Laboratory parameters studied

The patients were evaluated on the basis of pre-post absolute lymphocyte count (ALC), absolute neutrophil count (ANC), hemoglobin, and platelet count. Pancytopenia was defined as a deficiency in all three blood cell lineages. Anemia was defined as absolute reticulocyte count < 40,000/μL and hemoglobin <10g/μL. Neutropenia was defined as ANC < 1,000/μL; with severe neutropenia as ANC < 500/μL. Thromobcytopenia was defined as platelet count < 100,000/μL. Thrombocytosis was defined as platelet count > 750,000/μL.

Flow cytometric immunophenotyping and Vβ typing

Flow cytometric analysis of Vβ utilization was employed to quantify the size of T-LGL clone as previously described[26]. The results were expressed as the percentage of α/β CD4+ or CD8+ cells. Fresh peripheral blood was stained for Vβ flow cytometry according to manufacturer's instructions (IOTest Beta Mark kit; Beckman-Coulter, Fullerton, CA, USA). Due to incomplete coverage of the entire Vβ spectrum by the Vβ mAb set, further analysis was done and Vβ polymerase chain reaction (PCR) for Vβ families 6, 15 and 24 was performed. Clonotypic sequences of expanded Vβ and Jβ families were determined, and expanded CDR3 clonotypes were also detected.[26]

Immunophenotyping and Genotyping

HLA and killer immunoglobulin-like receptor (KIR) genotyping, KIR and KIR-L assignments, and genotyping of various cytokine polymorphisms were performed as previously described including TGF-β1 (codons 10 C/T, 25 G/C), TNF-α (−308G/A), interleukin-6 (IL-6) (−174 G/C), interleukin-10 (IL-10) (−1082 G/A, −819 C/T, and −592 C/A), IFN-γ (+874 T/A), CTLA4 (+45 A/G), FcγRIIIa(158V/F) and CD45 (77 C/G) [27].

RESULTS

Clinical characteristics of T-LGL patients

We have analyzed our cohort of 56 T-LGL patients with regard to several clinical parameters (Table 1). At the time of diagnosis 1/34 patient has been previously splenectomized for the initially presumed idiopathic thrombocytopenic purpura. At the time of referral we have verified that the proper diagnosis was T-LGL.

We dichotomized patients into two groups with respect to presence (n=34) or absence of splenomegaly (n=22). When these 2 groups were compared with regard to the types and severity of associated cytopenias, we have noted that patients with splenomegaly have more often bi- and pancytopenia (70.5%) than seen in patients lacking splenomegaly (27.2%; p=.

001). The median age in both the groups was 64 years. The median LGL count in the splenomegaly group was 1800/μL vs. 1130/μL in the group of patients with no splenomegaly (p=.410).

Associated autoimmune conditions included ulcerative colitis (n=1), rheumatoid arthritis (RA) (n=15), multiple sclerosis (MS) (n=1), systemic lupus erythematosus (SLE) (n=2), idiopathic pulmonary hypertension (n=1), and auto-immune thyroiditis (n=2). Interestingly several patients had a history of malignancies. The majority of the CTL populations expressed CD3, CD8, CD16, and CD57 antigens. Using Vβ flow cytometry, Vβ family expansion was detected in 54/56 patients. On average, Vβ expansions in constituted 64%± 30% of the Vβ repertoire within a given Vβ family A total of 86 immunodominant LGL clonotypes were identified (in some patients 2 co-dominant clones can be found). There was no difference in the Vβ clone size between splenomegalic patients (63%) and those without splenomegaly (64%; p=.882).

We also investigated HLA, KIR/KIR-ligand, and cytokine/cytokine receptor genotypes as previously described [27]. Comparison of patients with and without splenomegaly showed no difference in the KIR/KIR-ligand profile, HLA type, or frequency of cytokine and immunoregulatory receptor studied, including TGF-β1 (codons 10 C/T, 25 G/C), TNF-α (−308G/A), interleukin-6 (IL-6) (−174 G/C), interleukin-10 (IL-10) (−1082 G/A, −819 C/T, and −592 C/A), IFN-γ (+874 T/A), CTLA4 (+45 A/G), FcγRIIIa(158V/F) and CD45 (77 C/G)[27].

Clinical characteristics of splenectomized patients and outcomes

We further identified 15 patients who in the course of their disease underwent splenectomy; hematological and clinical outcomes were studied (Table 2). Diagnosis was established in all cases using immunophenotypic and flow cytometric evidence of Vβ expansions and TCR-γ rearrangement. Median age at splenectomy was 58 years and male/female ratio was 11/4. Associated conditions in these patients included RA, Grave's disease, FS, thyroid cancer, rectal carcinoma, melanoma, basal cell carcinoma, MDS, CLL, and monoclonal gammopathy of unknown significance (MGUS). The frequent association of T-LGL with B cell dyscrasias has been reported [28]. Due to the limited number of cases, no association was found between splenectomy and improvement in any co-associated condition. The indications for the splenectomy included symptomatic splenomegaly (5/15) and/or severe refractory cytopenias (pancytopenia, n=6; bicytopenia, n=3; single lineage cytopenias, n=5). Prior therapies were mostly symptomatic and supportive with granulocyte-colony stimulating factor (G-CSF), erythropoietin, or red cell transfusions. Two patients each received prior CHOP chemotherapy or cyclosporine, and 1 received oral cytoxan chemotherapy. Median spleen size was 1300 g and all patients showed clonal TCR-γ rearrangement in resected material; immunophenotype included positivity for CD3, CD5, CD8, CD57, CD16 and CD56. The majority of the patients underwent laparoscopic splenectomy (67%) with the remainder having a standard open procedure (33%). The presence of T-LGL was established/confirmed in resected spleens by histological methods and immunophenotyping.

There was no surgery related mortality in this cohort of T-LGL patients. Median follow- up of 719 days and the median survival time was 498 days (Figure 1A). Two patients died due to causes possibly related to splenectomised state and/or cytopenias (one of Gram negative sepsis and the other of EBV viremia with multiorgan dysfunction). Patient survival and length of follow-up is shown on the Kaplan Meier curve (Figure 1B). Blood parameter values for 10 of 11 patients showed improved counts following splenectomy and did not require further treatment for cytopenias, including achieving transfusion-independence. (Hgb, p=0.022, ANC, p=0.041 Plt, p=0.018; Figure 1). Molecular analysis of TCR-γ

utilization spectrum and Vβ flow cytometry showed persistence of the LGL clone in all patients tested (n=12) but no further expansion was observed.

DISCUSSION

To date, this is the largest reported study of splenectomized patients with T-LGL. Due to its low incidence, the therapies of T-LGL have often been empiric or based on case reports and retrospective single institution studies[11,29,30]. Most common indications for treatment include recurrent or life threatening infections, severe neutropenia, symptomatic anemia, thrombocytopenia or severe B symptoms. Although a therapeutic algorithm has been suggested[11,29], the role of several therapies has not been well defined and in many instances recommendations are empirically driven. Often cytopenias or systemic symptoms do not correlate with number of circulating T-LGL or bone marrow infiltration [11,31].

Inciting or sustaining signals of CTL clonal expansions in the etiology of T-LGL remain unknown. Its clinical course may be variable. Although, the involvement of the spleen is almost universal in T-LGL, its clinical significance remains uncertain. Splenectomy has been occasionally used as a therapeutic option in T-LGL patients whose counts remain refractory to medical measures e.g., in an attempt to decrease the transfusion-dependence. Systematic studies on this subject are not available; the largest series included 4 patients[13] and most of the reports contain individual cases [32–34].

Our investigations revealed that in most of the patients, splenectomy was necessitated either by refractory cytopenias requiring treatment and/or splenomegaly-related gastrointestinal complaints. Splenectomy in our cohort of T-LGL patients resulted in improvement in affected blood counts in all three lineages. None of the patients proceeded to the aggressive variant of T- LGL, with persistence of chronic disease, but clearly the procedure was not curative. The observed mortality included septic death and overwhelming EBV viremia can be either attributed to the primary disease or to splenectomized state of the patients.

Pathophysiologically, in addition to inherent hypersplenism, splenectomy could have a favorable impact on cytopenia as evidenced by increased frequency of bi- or pancytopenias in splenomegalic T-LGL[35]. Precise analysis of clonal size in the clinical course showed persistence of the malignant CTL clone post-splenectomy also suggesting that elimination of hypersplenism, rather than reduction in LGL-clone size (leukemic burden), contributes to the improvement of blood counts. Alternatively, removal of the spleen could result in a decreased disease burden (e.g., number of malignant LGLs) including associated autoimmune mechanisms not primarily related to LGL itself, such as autoantibodies or complement.

Significant limitations of our report are its retrospective nature, referral-bias and short follow up. However, prospective studies of splenectomy in T-LGL are unlikely possible in this rare condition. While the relatively short follow-up period post-splenectomy does not allow conclusions with regard to the long-term outcomes in this disease, the more immediate impact of the procedure on hematologic response proves to be favorable. Of note, cases referred for splenectomy were biased by clinical severity of symptoms and their refractoriness to conservative therapies.

In sum, the improvement in counts and low morbidity are encouraging to offer splenectomy as viable option to refractory and symptomatic cytopenias in T-LGL patients with splenomegaly.

Acknowledgments

Acknowledgements and Grant support:

Supported in part by a grant from R01 655365071402, U54 – 655365070704, K24 655365071503, to JPM.A grant from the Aplastic Anemia and MDS International Foundation (J.P.M.); and a generous gift from the Trotter family. Aaron D. Viny is a Howard Hughes Medical Institute Medical Research Training Fellow

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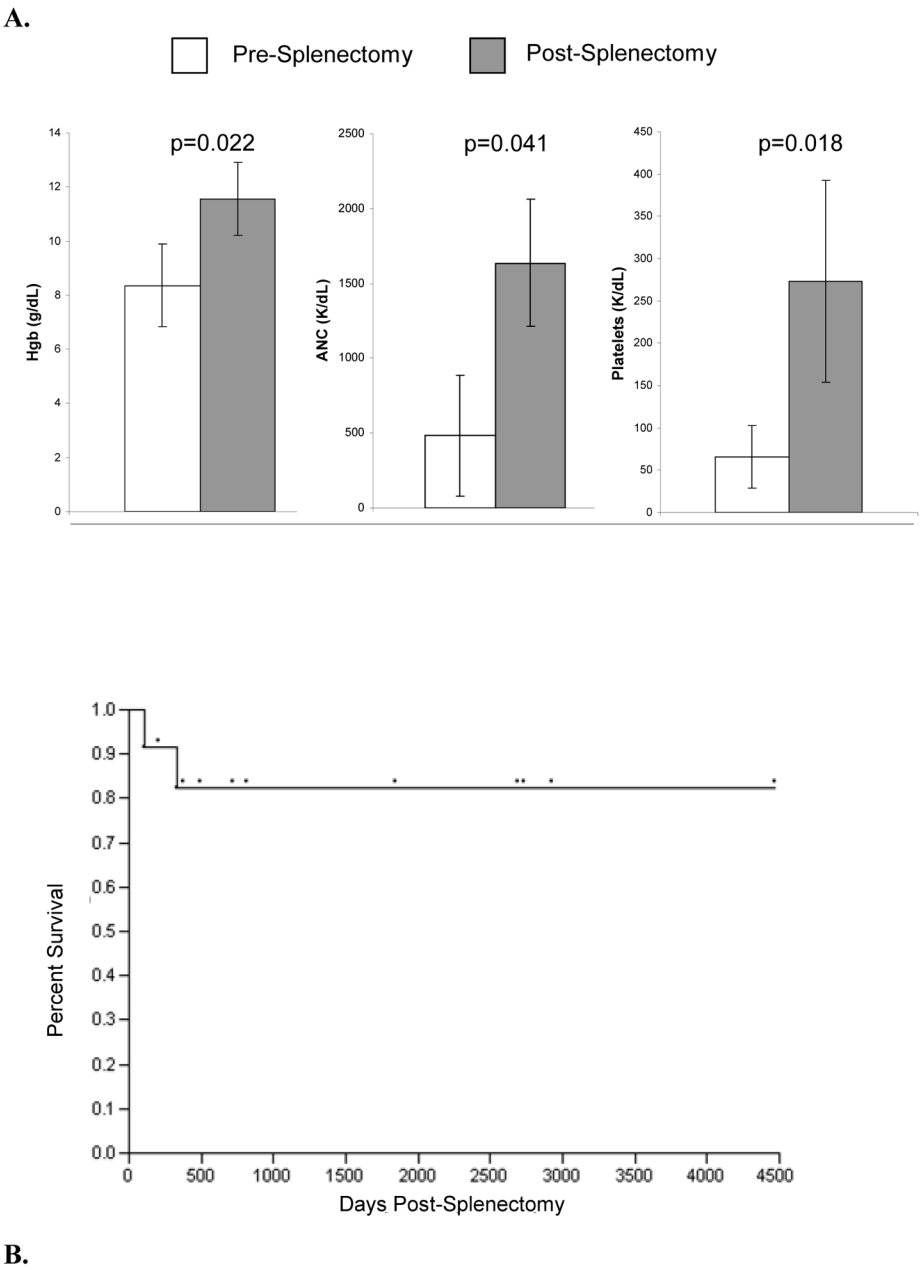

Figure 1. Effects of splenectomy on hematologic parameters affected by T-LGL

Hemoglobin (Hgb); Absolute Neutrophil Count (ANC) and platelets are depicted with standard error of the mean values pre and post splenectomy. **B.** Survival of patients with T-LGL who underwent splenectomy with median follow up 719 days the median survival time was 498 days, maximum survival at the end of this study was 4436 days for patient who received splenectomy at outside hospital.

Table 1

Clinical characteristics of patients with T-LGL

T-LGL Leukemia Cohort	Splenomegaly	No Splenomegaly	p-Value
Total Number in Cohort (Female)	34 (16)	22 (8)	0.61
Median Age at Diagnosis in Years (Range)	64 (28–81)	64 (31–78)	0.88
Single Lineage Cytopenia	10/34 (29%)	15/22 (68%)	<0.01
Anemia (Hgb<10g/dL)	8/34 (24%)	9/22 (41%)	0.17
Neutropenia	1/34 (3%)	5/22 (23%)	0.02
Thrombocytopenia	1/34 (3%)	1/22 (5%)	0.75
Bicytopenia	16/34 (47%)	3/22 (14%)	<0.01
Pancytopenia	8/34 (24%)	3/22 (14%)	0.36
Median LGL Count (Range)	1800 (100–20575)	1130 (100–7410)	0.41
Median CD4:CD8 (Range)	0.35 (0.03–3.00)	0.31 (0.04–1.39)	0.51
Median % Vβ expansion (Range)	63 (19–98)	64 (11–90)	0.88

Splenomegaly was identified by palpation or clinical suspicion and confirmed by ultrasound or CT scan.

Table 2

Clinical Features of Splenectomized T-Cell patients

Pt	Age	Sex	Presentation	Prior Therapy	Reason for Splenectomy	Spleen Size	Ref.Dx	Conf.Dx	Associated Conditions
1	58	F	GI symptoms, Anemia	Cytoxan,	Transfusion-dependant anemia	N/a	LGL	T-LGL	MGUS, Thyroid ca
2	43	M	Weight loss, Splenomegaly, night sweats	CHOP	Diagnostic	500 g	LGL	T-LGL	Sarcoidosis, CMV IgG Ab +
3	74	M	Pancytopenia, fatigue, GI symptoms	Cyclosporine	Pancytopenia with normal BM and high retic count	515 g	MDS	T-LGL	Hypothyroidism
4	52	M	Neutropenia, thrombocytopenia, splenomegaly	G-CSF	Severe thrombocytopenia, splenomegaly	5800 g	LGL	T-LGL	Multiple Myeloma
5	33	M	Pancytopenia	Erythropoeitin, Transfusions	Pancytopenia	936 g	MDS	T-LGL	Graves, Gilbert's Disease
6	62	F	Neutropenia, lymphocytosis	G-CSF	Neutropenia with hypercellular bone marrow	500 g	LGL	T-LGL	RA
7	53	M	Neutropenia, anemia	G-CSF	Transfusion-dependant anemia	804 g	CLL	T-LGL	
8	70	M	Neutropenia, splenomegaly	G-CSF	Neutropenia	N/a	LGL	T-LGL	RA
9	39	F	Pancytopenia	G-CSF	Pancytopenia with hypercellular bone marrow	1668 g	LGL	T-LGL	Autoimmune hepatitis
10	58	M	Anemia	CHOP, Erythropoeitin, Transfusions	Transfusion-dependant Anemia	1000 g	LGL	T-LGL	Rectal Carcinoma
11	65	M	Leukopenia, thrombocytopenia	Transfusions	Thrombocytopenia, h/o splenic bleeding	570 g	LGL	T-LGL	
12	52	M	Pancytopenia	G-CSF	GI symptoms	570 g	LGL	T-LGL	EBV viremia, Parvovirus B19 IgG+
13	80	F	Neutropenia	G-CSF	Neutropenia with normal BM, GI symptoms	186 g	Neutropenia	T-LGL	RA, melanoma, BCC
14	34	M	Pancytopenia	Erythropoeitin, Transfusions	Pancytopenia with splenomegaly	3700 g	Pancytopenia	T-LGL	
15	58	M	Pancytopenia	Cyclosporine, Splenectomy	Thrombocytopenia	340 g	ITP/CLL	T-LGL	

N/a: Not available; RA: Rheumatoid Arthritis;CLL: Chronic Lymphocytic Leukemia; BCC: Basal Cell Carcinoma; ITP: Idiopathic Thrombocytopenia Purpura; Ref. Dx: Referral Diagnosis; Conf.Dx: Confirmatory diagnosis; Diagnosis of MDS based on WHO classification.

Table 3

Pre-splenectomy and Post-splenectomy laboratory cell counts of various blood parameters tested.

Pre-Splenectomy Counts					Post-Splenectomy Counts			
Pt #	**ALC**	**ANC**	**Hgb**	**Plt**	**ALC**	**ANC**	**Hgb**	**Plt**
1	330	122	8	403	1390	1770	13.1	273
2	197	234	15.7	285	2760	4110	14.3	285
3	610	1200	10.2	120	3300	930	10.5	434
4	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
5	N/a	N/a	N/a	N/a	3200	1760	14.7	250
6	3460	89	13.2	297	2840	1770	13.2	247
7	4180	620	8.6	175	17380	1800	10.7	444
8	N/a	N/a	N/a	N/a	4510	340	12.8	181
9	750	579	9.3	57	7490	2120	13.3	400
10*	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
11	2100	240	11.1	83	2800	680	12	174
12*	610	380	11.8	51	1530	1790	13.8	12
13	1390	450	11.8	154	4330	1041	12.2	328
14	900	99	5.7	63	3480	1953	10.2	156
15	550	740	8.7	7	5930	7710	15.1	202

ALC, Absolute lymphocyte count; ANC Absolute neutrophil count; Hgb, Hemoglobin; Plt, Platelet count;

*deceased;

N/a, Not available

Table 4

Literature review of reports of splenectomized T-Cell LGL patients

Citation	T-LGL	Splenomegaly	Country	n	Reason for Splenectomy	Findings
Loughran et al 1987[13]	Y	Y	USA	4	Neutropenia	Increase in neutrophil counts, 2/4 sustained, 1 patient died due to aggressive disease
Furukawa et al. 1991[32]	Y	Y	Japan	1	Thrombocytopenia	Platelets returned to nl after splenectomy, 2 years later patient died secondary to sepsis -DIC
Coad JE et al. 1993[36]	Y	Y	UK	4	Therapy-resistant disease and therapeutic splenectomy	Retrospective study of 70 heterogenous patients with chronic lymphoproliferative disorders.
Gentile TC et al 1996[33]	Y	Y	USA	1	AIHA	Increase in Hb to normal level
Brinkman K et al 1998[34]	Y	Y	Netherlands	1	N/A	Treatment failure with splenectomy and remission with cyclosporin A
Nowakowski et al 2005[35]	Y	Y	USA	4	Therapeutic for Splenomegaly	Pts. in KIR/HLA-I mismatch group 4 pts. required therapeutic splenectomy. Outcomes not reported
CCTCI*	Y	Y	USA	15	Symptomatic cytopenias, Splenomegaly	2/15 died. 13/15 sustained response

*CCTCI-Cleveland Clinic Taussig Cancer Institute series;

Y-Yes ;N/A- Not available