T-Cell Large Granular Lymphocytic Leukemia with Atypical Immunophenotypes: A Single Center Retrospective Analysis of 17 Cases

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Research Article

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Abstract

Purpose

T-cell large granular lymphocytic leukemia (T-LGLL) is characterized by expansion of cytotoxic T cells expressing αβ T cell receptor (TCR), CD2, surface CD3, CD8, CD57 as well as cytotoxic molecules. Atypical immunophenotypes of T-LGLL, including γδ TCR and CD4, reported in a small subset, remains to be well-defined.

Methods

We retrospectively analyzed immunophotypes and clinicopathologic features of 96 T-LGLL cases.

Results

We found a total of 17 cases with atypical immunophenotypes including 9 TCRγδ + cases and 8 CD4+ TCRαβ + cases. Pure red cell aplasia was less common in atypical immunophenotypes patients compared to that of typical immunophenotypes [0/17 (0%) vs. 26/79 (32.9%), p=0.005]. STAT3 mutations were also less frequent in atypical immunophenotypes cases, although accompanied with marginal significance (p=0.086).

Conclusion

Patients with atypical immunophenotypes showed a similar survival outcome to that of typical T-LGLL immunophenotypes. Additional efforts were needed to better understand the pathogenesis of these rare atypical immunophenotypes T-LGLL cases.

Introduction

Large granular lymphocyte (LGL) leukemia is a rare lymphoproliferative disease with three recognized subgroups: T-cell leukemia, chronic natural killer (NK) cell lymphocytosis, and NK cell leukemia (Lamy et al. 2017). Approximately 85% of LGL leukemia cases are of the T-LGL subtype, and less than 10% of cases are described as chronic NK-LGL leukemia.T-cell large granular lymphocytic leukemia (T-LGLL) is a subtype of T-cell neoplasm characterized by persistence of increased large granular cells in the peripheral blood. In addition to the peripheral blood and bone marrow, the leukemia cells of T-LGLL also infiltrate the spleen and liver, leading to splenomegaly and hepatomegaly in some cases. Patients suffering from T-LGLL have a wide variety of clinical presentations, mostly presenting with cytopenia including neutropenia, anemia and thrombocytopenia, and autoimmune diseases, such as rheumatoid arthritis. The typical abnormal lymphocytes in the circulation show moderate to abundant cytoplasm with fine or course azurophilic granules(Lamy et al. 2017). The characteristic immunophenotype of T-LGLL is CD2+,

CD3+, CD8+, CD57+ and αβ T cell receptor (TCR)+. Additionally, T-LGLL cells also express cytotoxic markers including TIA1, granzyme B, and granzyme M. The etiology of T-LGLL is largely unexplored. Somatic STAT3 mutations have been identified approximately in one third cases of T-LGLL, suggesting the importance of activation of STAT3 pathway in the pathogenesis of T-LGLL (Koskela et al. 2012). The latest WHO classification in 2016 highlights the discovery of signal transducer and activator of transcription 3 (STAT3) and STAT5b mutations (Swerdlow et al. 2016). Most cases of T-LGLL show an indolent clinical course. Treatment should not be initiated until the presence of treatment indications, which include anemia, severe neutropenia, symptomatic splenomegaly, and others (Qiu et al. 2016).

Although cases of T-LGLL are usually CD8+ and express αβTCR, there are variants with atypical immunophenotypes (Lima et al. 2003; Olteanu et al.2010; Yabe et al. 2015). Atypical immunophenotypes include CD4+TCRαβ+, CD8+ TCRγδ + and CD4-CD8- TCRγδ+ (Yabe et al. 2015; Shaw et al. 2008). The cases series of T-LGLL with atypical immunophenotypes have been reported in several studies (Lima et al. 2003;Yabe et al. 2015;Shaw et al. 2008; Sandberg et al. 2006; Garrido et al. 2007). Yabe *et al.* analyzed 14 patients with TCRγδ + T-LGLL, and found these patients showed lower neutrophil counts, lower platelet counts and a higher frequency of the CD4-CD8- immunophenotype, compared to the counterparts with TCRαβ + T-LGLL. Additionally, patients with TCRγδ + T-LGLL were more likely to develop rheumatoid arthritis (RA)(Yabe et al. 2015). CD4+ T-LGLL showed a more indolent clinical course. In a cohort of 8 patients with CD4+ T-LGLL, with a median follow-up of 29 months, none of these patients required treatments for T-LGLL. And CD56, uncommonly detected on the cell surface of CD8+ T-LGLL cells, was uniformly expressed by the CD4+ T-LGLL cells (Olteanu et al. 2008). These findings suggested that CD4+ T-LGLL might be distinct from CD8+ T-LGLL.

Previous studies have proved that there were differences between Asian patients with T-LGLL and western patients with T-LGLL (Kwong et al.2010). For example, there was a significantly higher incidence of pure red cell aplasia (PRCA) and a much lower incidence of RA in Asian patients with T-LGLL than that in western patients with T-LGLL (Qiu et al.2013). T-LGLL cases with atypical immunophenotypes have not been systematically investigated. There are no data on the pedigree, clinical and biological characteristics of these atypical immunophenotypic cases. Therefore, in the present study, we retrospectively analyzed the prevalence, the spectrum as well as the clinical and laboratory findings of cases with atypical immuphenotypes in a cohort of Chinese patients with T-LGLL. We also determined whether there are differences in clinical and laboratory characteristics and clinical results between atypical immunophenotypes cases and typical immunophenotypes cases.

Materials And Methods

Patients with T-LGLL who were diagnosed from 2009 to 2017 were included in this study. The diagnosis of T-LGLL was based on the 2008 World Health Organization (WHO) (Swerdlow et al.2008). Cases with large granular lymphocytes less than $2{\cdot}10^9$/L, when the lymphocytes showed typical morphologic and immunophenotypic features, were also diagnosed as T-LGLL if the clonality of these lymphocytes could be demonstrated. Clinical and laboratory data were then collected for analysis. Appropriate T-LGLL

consents were obtained from all donors prior to specimen collection in accordance with the Declaration of Helsinki and approved by the ethics committees of the First Affiliated Hospital of Nanjing Medical University. Immunophenotyping was performed on peripheral blood or bone marrow specimens. Antibodies specific for these following antigens were used including CD3, CD2, CD5, CD7, CD4, CD8, CD16, CD56, CD57, TCR αβ and TCR γδ. These antibodies were incubated with samples from peripheral blood or bone marrow in different combinations. Additionally, the β Mark TCR Vβ Repertoire Kit was utilized for the quantification of the TCR Vβ repertoire of the T lymphocytes. This kit contains mixtures of conjugated TCR Vβ antibodies corresponding to a total of 24 different specificities, which cover approximately 70% of all the normal human TCR Vβ repertoire. The determination of these 24 Vβ expressions was done in 8 tubes, with one tube permitting the detection of 3 different Vβ expressions by using three different antibodies labeled with fluorescein isothiocyanate (FITC), phycoerythrin (PE) and FITC plus PE, respectively. Other antibodies to CD3, CD4 and CD8, which were conjugated to different fluorophores were added in each tube. After incubation, red blood cells were lysed using Tris-NH_4Cl solution (Qiu et al.2014; Fan et al.2015). Then the samples were run on the FACSCalibur instrument (BD Biosciences) and the CellQuest software was used to conduct the data analysis.

The genomic DNA was purified from the peripheral blood or bone marrow samples using the QIAamp DNA Blood Mini Kit. The PCR amplification of TCRβ and TCRγ was performed accroding to previously reported method (Qiu et al.2014). After amplification, heteroduplex analysis and GeneScanning analysis were used for the analysis of clonality of the PCR products. For STAT3 mutational status analysis, exon 20 an 21 of STAT3 were sequenced by Sanger sequencing. The amplification, sequencing as well as data analysis were performed according to a previously described protocol (Qiu et al.2014)..

Pearson chi-squared test and Fisher's exact test were used as appropriate. Overall survival (OS) was defined as time from the diagnosis until death or last follow-up. Kaplan-Meier method was used for plotting Survival curves and log-rank test was used for comparison. Graphpad Prism 6 (GraphPad Software, San Diego, CA) as well as SPSS (version 19.0) software (IBM Corporation, Armonk, NY, USA) were used for data analysis. P-value less than 0.05 was defined as statistically significant.

Results

A total of 96 patients with T-LGLL including 49 males and 47 females were identified (details in supplementary table S1). The median age was 59 years old(range: 28-89 years old). The baseline clinicopathologic characteristics were showed in Table 1. At the time of presentation, 71 patients (71/96, 74.0%) had symptoms, while fatigue was the most common one (53/96, 55.2%). In our cohort, only 4 cases (4/94, 4.2%) had rheumatoid arthritis. The median large granular lymphocytes count was 2.94×10^9/L (range: 0.2-19.75×10^9/L). Neutropenia, thrombocytopenia and anemia were found in 49 (51.0%), 16 (16.7%), and 53 (55.2%) cases, respectively. A total of 26 patients were confirmed to have PRCA by bone marrow examination. TCR clonal rearrangement was confirmed in all cases. STAT3 sequencing was performed in 64 patients, in which 7 patients had STAT3 mutations.

Table 1
Clinical, laboratory, and molecular features of 96 patients with T-cell large granular lymphocytic leukemia.

Parameters	N[a] (%)*
Gender	
Male	49 (51.0)
Female	47 (49.0)
Age	
≥60 years	45 (46.9)
<60 years	51 (53.1)
Fatigue	53 (55.2)
B symptoms	16 (16.7)
Infection	11 (11.5)
Large granular lymphocyte count (·109/L)	2.94 (0.27-19.75)
Absolute lymphoctye count (·109/L)	3.71 (0.52-23.03)
Absolute neutrophil count (·109/L)	1.53 (0.21-9.18)
Hemoglobin (g/L)	88.5 (32-165)
Platelet count (·109/L)	179.5 (11-465)
Absolute neutrophil count ≤1.5 × 109/L	49 (51.0)
Absolute neutrophil count≤0.5 × 109/L	9 (9.4)
Hemoglobin ≤100 g/L	53(55.2)
Platelet count ≤100 × 109/L	16 (16.7)
Lactate dehydrogenase ≥271 U/L	13 (13.5)
β2-microglobulin ≥2.53 mg/L	62 (64.6)
Ferritin ≥336.2 ng/ml	38(39.6)
Splenomegaly	22 (22.9)
Hepatomegaly	4 (4.2)
Lymphadenopathy	11 (11.5)
Pure red cell aplasia	26 (27.1)
Rheumatoid arthritis	4 (4.2)

Parameters	N[a] (%)*
Immune thrombocytopenia	3 (3.1)
Systemic lupus erythematosus	3 (3.1)
Sjogren's syndrome	2 (2.1)
Demyelinating diseases of nervous system	2 (2.1)
Autoimmune hemolytic anemia	1 (1.0)
Hypothyroidism	1 (1.0)
Hyperthyroidism	1 (1.0)
Antiphospholipid syndrome	1 (1.0)
Nephrotic syndrome	1 (1.0)
B-cell malignant lymphoma	3 (3.1)
Myelodysplastic syndromes	1 (1.0)
Megaloblastic anemia	1 (1.0)
Multiple myeloma	1 (1.0)
Positive STAT3 mutation	7 (7.3)
Chromosomal abnormalities	12 (12.5)

Seventy-nine patients and 17 patients had typical immunophenotypes and atypical immunophenotypes, respectively. These 79 cases with typical immunophenotypes were CD8+CD4-TCRαβ + . In 17 cases with atypical immunophenotypes, 8 cases were CD4+CD8-TCRαβ + and 9 cases were TCRγδ + . In TCRγδ + cases, 7 cases were both CD4 and CD8 negative while the other two cases were CD4 negative and CD8 positive.

The clinical and laboratory findings of patients T-LGLL with typical and atypical immunophenotypes were summarized in Table 2. We compared the clinical and laboratory characteristics of patients with atypical immunophenotypes and those with typical immunophenotypes. We found that presence of PRCA was more frequent in patients with typical immunophenotypes than those with atypical immunophenotypes [26/79 (32.9%) vs. 0/17 (0%), p=0.005]. In addition, compared with cases with atypical immunophenotypes, cases with typical immunophenotypes had no difference in STAT3 mutations [7/52 (13.5%) vs 0% (0/12), p=0.331]. There were no significant differences in other clinical or laboratory parameters between these two groups.

Table 2
Comparison of baseline characteristics between cases with typical and atypical immunophenotypes.

Parameters	T-LGLL with typical immunophenotype	T-LGLL with atypical immunophenotype	*p*
Gender			0.863
Male	50.6 (40/79)	41.2 (9/17)	
Female	49.4 (39/79)	58.8 (8/17)	
Age			0.987
≥60 year	43.0 (37/79)	41.2 (8/17)	
<60 years	57.0 (42/79)	58.8 (9/17)	
Absolute lymphoctye count ≥2.5×10^9/L	73.1 (52/79)	52.9 (13/17)	0.394
Absolute neutrophil count ≤1.5×10^9/L	52.0 (41/79)	41.2 (7/17)	0.423
Hemoglobin ≤100 g/L	58.2 (46/79)	41.2 (7/17)	0.200
Platelet count ≤100×10^9/L	17.7 (14/79)	11.8 (2/17)	0.729
Lactate dehydrogenase ≥271 U/L	15.2 (12/79)	5.9 (1/17)	0.453
β_2-microglobulin≥2.53 mg/L	67.1 (53/79)	52.9 (9/17)	0.269
Ferritin ≥336.2 ng/ml	43.0 (34/79)	23.5 (4/17)	0.136
Chromosomal abnormalities	11.4 (9/79)	17.6 (3/17)	0.440
Fatigue	57.0 (45/79)	47.1 (8/17)	0.456
B symptoms	17.7 (14/79)	11.8 (2/17)	0.729
Rash	3.8 (3/79)	5.9 (1/17)	0.548
Splenomegaly	22.8 (18/79)	23.5 (4/17)	1.000
Pure red cell aplasia	32.9 (26/79)	0 (0/17)	0.005*
Positive STAT3 mutation	13.7 (7/52)	0 (0/12)	0.331

We then compared the clinical and laboratory features of TCRγδ + T-LGLL with TCRαβ + T-LGLL (Table 3). The frequency of PRCA was slightly lower in patients with TCRγδ + T-LGLL than in those with TCRαβ + T-LGLL [0%(0/9) vs. 30.4%(26/87),p=0.108]. The frequencies of female, STAT3 mutation, fatigue, mouth ulcer, hepatomegaly and arthralgia were lower in TCRγδ + cases than in TCRαβ + cases, although there

was no statistical significance. There were no differences in other parameters between TCRγδ + cases and TCRαβ + cases. We also explored the distinction between CD4+ cases and CD4-TCRαβ + cases (Table 4). The prevalence of PRCA was slightly higher in patients with CD4+ T-LGLL than in those with CD4-TCRαβ + T-LGLL [29.9% (26/79) vs. 0% (0/8), p=0.099]. The frequencies of female, anemia, mouth ulcer and STAT3 mutation were also lower in CD4+ T-LGLL than in CD4-TCRαβ + T-LGLL, although this was not statistically significant. No differences in other clinical or laboratory features between patients with CD4+ T-LGLL and patients with CD4- T-LGLL.

Table 3

Comparison of baseline characteristics between cases with **TCRγδ$^+$ T-LGLL** and **TCRαβ$^+$ T-LGLL.**

Parameters	**TCRγδ$^+$ T-LGLL(%)**	**TCRαβ$^+$ T-LGLL(%)**	***p***
Gender			0.487
Male	66.7(6/9)	49.4(43/87)	
Female	33.3(3/9)	50.6(44/87)	
Age			1.000
≥60 years	44.4(4/9)	42.5(41/87)	
<60 years	55.6(5/9)	57.5(46/87)	
Absolute lymphoctye count ≥2.5×10^9/L	66.7(6/9)	67.8(59/87)	1.000
Absolute neutrophil count ≤1.5 × 10^9/L	44.4(4/9)	50.6(44/87)	1.000
Hemoglobin ≤100 g/L	55.6(5/9)	55.2(48/87)	1.000
Platelet count ≤100 × 10^9/L	11.1(1/9)	17.2(15/87)	1.000
Lactate dehydrogenase ≥271 U/L	11.1(1/9)	13.8(12/87)	1.000
β2-microglobulin≥2.53 mg/L	55.6(5/9)	65.5(57/87)	0.716
Ferritin ≥336.2 ng/ml	33.3(3/9)	40.2(35/87)	1.000
Chromosomal abnormalities	11.1(1/9)	12.6(11/87)	1.000
Fatigue	55.6(5/9)	55.2(48/87)	1.000
B symptoms	11.1(1/9)	17.2(15/87)	1.000
Rash	0(0/9)	4.6(4/87)	1.000
Splenomegaly	22.2(2/9)	23.0(20/87)	1.000
Pure red cell aplasia	0(0/9)	29.9(26/87)	0.108
Positive STAT3 mutation	0(0/7)	12.3(7/57)	0.100
LGLL, large granular leukemia; TCR, T cell receptor.			

Table 4

Comparison of baseline characteristics between cases with $CD4^+$ T-LGLL and $CD4^-TCR\alpha\beta^+$T-LGLL.

Parameters	$CD4^+$ T-LGLL(%)	$CD4^-TCR\alpha\beta^+$T-LGLL(%)	*p*
Gender			0.713
Male	37.5 (3/8)	50.6 (40/79)	
Female	62.5 (5/8)	49.4 (39/79)	
Age			1.000
≥60 years	37.5 (4/8)	43.0 (37/79)	
<60 years	62.5 (4/8)	57.0 (42/79)	
Absolute lymphoctye count ≥2.5×10^9/L	87.5 (7/8)	65.8 (52/79)	0.428
Absolute neutrophil count ≤1.5×10^9/L	37.5 (3/8)	51.9 (41/79)	0.484
Hemoglobin ≤100 g/L	25.0 (2/8)	58.2 (46/79)	0.132
Platelet count ≤100×10^9/L	12.5 (1/8)	17.7 (14/79)	1.000
Lactate dehydrogenase ≥271 U/L	0 (0/8)	15.2 (12/79)	0.592
β2-microglobulin≥2.53 mg/L	50.0 (4/8)	67.1 (53/79)	0.439
Ferritin ≥336.2 ng/ml	12.5 (1/8)	43.0 (34/79)	0.136
Chromosomal abnormalities	25.0 (2/8)	11.4 (9/79)	0.266
Fatigue	37.5 (3/8)	57.0 (45/79)	0.458
B symptoms	12.5 (1/8)	17.7 (14/79)	1.000
Rash	12.5 (1/8)	3.8 (3/79)	0.325
Splenomegaly	25.0 (2/8)	22.8 (18/79)	1.000
Pure red cell aplasia	0 (0/8)	32.9 (26/79)	0.099
Positive STAT3 mutation	0 (0/5)	13.5 (7/52)	1.000
LGLL, large granular leukemia; TCR, T cell receptor.			

In patients who received first-line therapy, the overall response rate (ORR) in patients with atypical immunophenotypes was higher than that in patients with typical immunophenotype (88.9%(8/9) vs. 68.4%(39/57), p=0.428), although there was no statistical significance. The ORR was 83.3% (5/6) in patients with TCRγδ + T-LGLL, compared to 70.0% (42/60) in patients with TCRαβ + T-LGLL, however, the difference was not statistically significant (p=0.664). The ORRs in CD4-TCRαβ + T-LGLL patients and CD4+ T-LGLL patients were 68.4 % (39/57) and 100% (3/3), respectively (p=0.547). The overall survival

(OS) of patients with typical immunophenotype and those with atypical immunophenotype were similar (4-year OS: 87% vs. 94%, p=0.174, Figure.1A). The median survival was not reached in each group. The OS of patients with TCRγδ + T-LGLL was also similar to that of patients with TCRαβ + T-LGLL (4-year OS: 89% vs. 88%, p=0.623, Figure.1B). The survival of patients with CD4+ T-LGLL cases was not statistically different to that of CD4-TCRαβ + T-LGLL cases (4-year OS: 100% vs. 87%,p=0.173, Figure.1C).

Discussion

In the present study, we analyzed the clinical pathologic characteristics of 96 cases of T-LGLL. The frequency of PRCA in our cohort was significantly higher than that in the patients with T-LGLL from western countries. The incidence of rheumatoid arthritis is relatively low. The above findings were consistent with the study by Kwong *et al.*, in which showed that Asian patients with T-LGLL were more likely to PRCA and much less likely to have RA (Kwong et al.2010).

By analyzing the immunophenotypes of these cases, we identified 17 T-LGLL cases with atypical immunophenotypes, including TCRγδ + phenotype and CD4 expression. The frequency of TCRγδ + LGLL (9/96) in our cohort was similar to that in other studies (Sandberg et al.2006). It is important to differentiate TCRγδ + T-LGLL from other entities with aggressive clinical process, in which hepatosplenic T cell lymphoma (HSTCL) is the most important one. Clinical and immunophenotypic features are useful for distinguishing HSTCL from TCRγδ + T-LGLL. Patients with HSTCL usually develop rapidly in clinical practice, even leading to secondary hemophagocytic syndrome. In our cohort, only two patients with TCRγδ + T-LGLL had mild splenomegaly and only one patient with TCRγδ + T-LGLL presented with thrombocytopenia. Immunophenotypically, TCRγδ + T-LGLL is usually CD57+ and granzyme B positive, while HSTCL is always CD57 negative and granzyme B negative. The clinical and laboratory features lead to the diagnosis of TCRγδ + T-LGLL in these 9 cases. In our cohort, in contrast to patients with TCRαβ + T- LGLL, none of patients with TCRγδ + T-LGLL had PRCA, indicating TCRαβ + T-LGLL and TCRγδ + T-LGLL may have different clinical manifestations. According to a previous study, patients with TCRγδ + LGLL were more likely to have RA and lower platelet count, compared to those with TCR αβ + LGLL (Yabe et al. 2015;Sandberg et al. 2006). However, in our cohort, none of patients with TCRγδ + LGLL have RA and only one patient with TCRγδ + LGLL had thrombocytopenia, which indicated that cases of TCRγδ + LGLL in Asia may be clinically different from those in the western countries.

Eight patients in our cohort were found to have CD4+ T-LGLL and these cases all expressed TCRαβ. The CD4+ phenotype have been reported in a minority of T-LGLL cases (Lima et al.2003; Olteanu et al.2008), however, the exact prevalence of CD4+ phenotype in cases of T-LGLL was unknown. CD4+ T-LGLL needs to be differentiated from other CD4+ mature T cell leukemias including T cell prolymphocytic leukemia, Sézary Syndrome and adult T cell leukemia/lymphoma. In our cohort, these 8 CD4+ cases could be readily distinguished from CD4+ T cell leukemias based on clinical, morphologic, and immunophenotypic characteristics. Besides, anemia and PRCA were less common in patients with CD4+ T-LGLL, when compared to those with CD4- T-LGLL, suggesting CD4+ T-LGLL was more clinically indolent. It is reported that CD4+ T-LGLL patients do not have cytopenia or autoimmune phenomena but frequently have other

maliganancies. In consistent with previous studies[5,6], cytopenia was infrequent in patients with CD4+ T-LGLL in our cohort. Additionally, autoimmune phenonema including RA and PRCA were not observed in these 8 patients. However, in contrast to previous studies in the western countries (Olteanu et al.2008), patients with CD4+ T-LGLL in our cohort did not have additional maligancies.

STAT3 mutations were identified in approximately 40% of T-LGLL cases, suggesting dysregulated STAT3 signal pathway was involved in the pathogenesis of T-LGLL (Koskela et al.2012). The mechanisms underlying the pathogenesis of T-LGLL cases with atypical immunophenptypes remain elusive. Gene expression analysis revealed that compared with normal TCRγδ + T cells, tumor cells of TCRγδ + T-LGLL patients showed abnormal expression of genes involved in cell apoptosis and proliferation, indicating that survival and proliferation disorders may be the development mechanism of TCRγδ + T-LGLL (Kallemeijn et al. 2017). Due to the lack of the next generation sequencing studies of TCRγδ + T-LGLL, the genetic lanscape of TCRγδ + T-LGLL remains to be determined. Interestingly, TCRγδ + T-LGLL cases showed a restricted usage of Vγ and Vδ families with a similar pattern as normal TCRγδ + T cell, suggesting antigen stimulation might be involved in the pathogenesis of TCRγδ + T-LGLL (Sandberg et al.2006). Regarding CD4+ T-LGLL, STAT5B mutations were identified in about half of the cases, suggesting STAT5B activation might be responsible for the pathogenesis of CD4+ T-LGLL (Andersson et al.2016). Over one third of the CD4+ T-LGLL cases expressed monoclonal TCR-Vbeta13.1 (Lima et al.2003;Garrido et al. 2007). Interestingly, the sequencing of TCR segments in these TCR-Vbeta13.l-restricted T cells showed evidence of the use of common TCRV-beta gene segments, suggesting the expansion of the CD4+ positive T cells may be driven by a common antigen.

Conclusions

In conclusion, a small proportion of T-LGLL cases in the Chinese population harbored atypical immunophenotypes including TCRγδ expression and CD4 expression. These cases with atypical immunophenotypes exhibited similar indolent clinical courses with T-LGLL patients with typical immunophenotypes. However, these cases with atypical immunophenotypes did show some features that were distinct from cases with typical immunophenotypes. More genetic and biologic studies were warranted to define the mechanisms underlying the pathogenesis of the cases with atypical immunophenotypes.

Abbreviations

fluorescein isothiocyanate - FITC

hepatosplenic T cell lymphoma - HSTCL

natural killer - NK

Overall survival - OS

overall response rate - ORR

phycoerythrin - PE

pure red cell aplasia - PRCA

rheumatoid arthritis - RA

signal transducer and activator of transcription 3 - STAT3

T. cell large granular lymphocytic leukemia - T-LGLL

T cell receptor - TCR

World Health Organization - WHO

Declarations

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

Jing-jing Guo and Lei Cao analyzed and interpreted the patients’ data regarding the T-LGLL disease. Hua-yuan Zhu, Yi Miao, Xin-yi Du, Li Wang and Wei Xu participated in the treatment of these patients and collection of clinical information. Jian-yong Li and Lei Fan designed and guided the research.

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Ethics approval and consent to participate

Appropriate T-LGLL consents were obtained from all donors prior to specimen collection in accordance with the Declaration of Helsinki and approved by the ethics committees of the First Affiliated Hospital of Nanjing Medical University.

Consent for publication

All co-authors have seen the manuscript and approved to submit to your journal for publication.

Availability of data and materials

The authors uploaded the supplementary tables for details.

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Figures

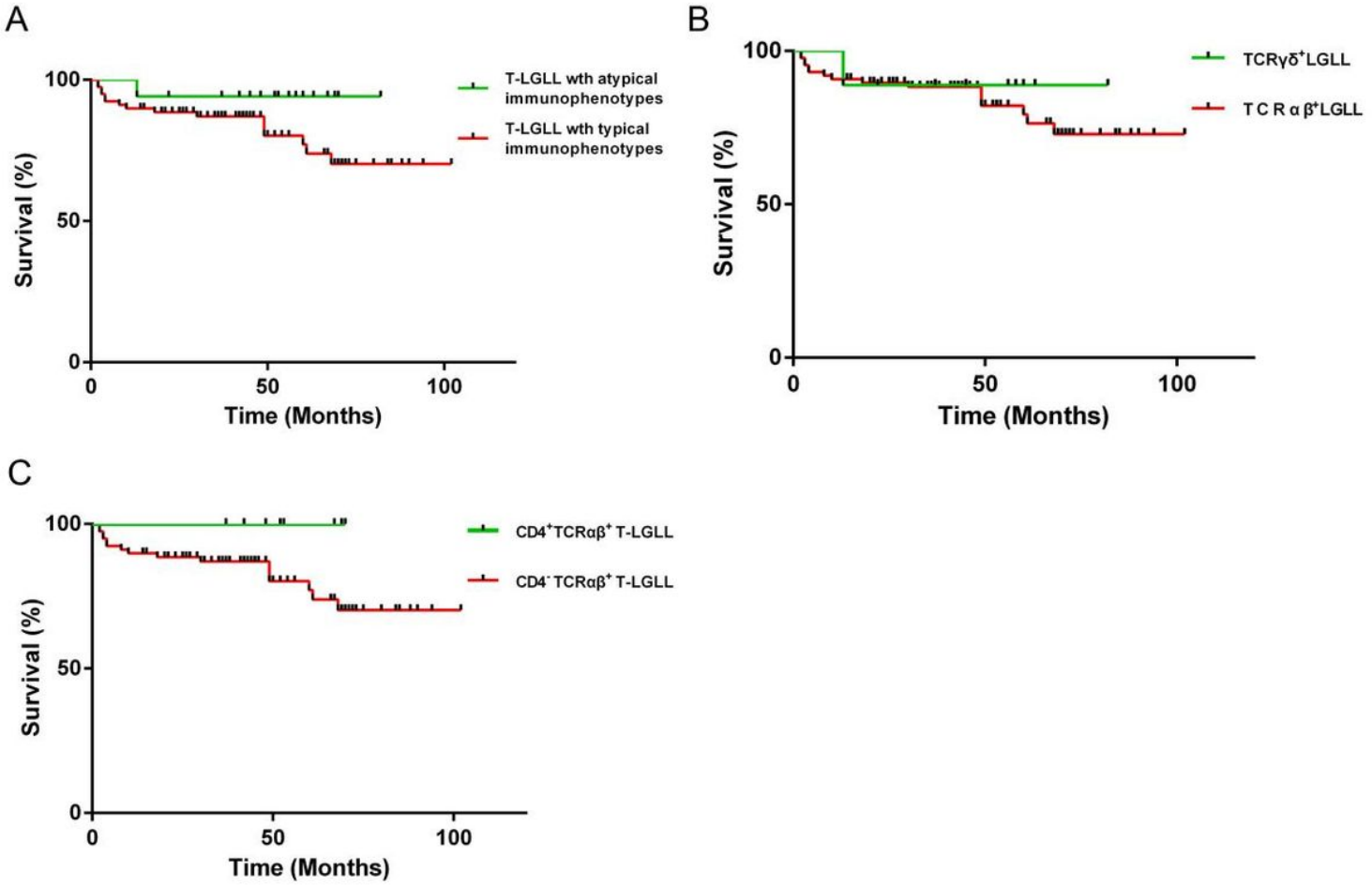

Figure 1

Survival outcomes of T-LGLL patients A. The impact of atypical immunophenotypes on the survival outcome; B. Survival outcomes of patients with TCRαβ+ T-LGLL and patients with TCRγδ+ T-LGLL; C. Survival outcomes of patients with CD4+ T-LGLL and patients with CD4-TCRαβ+ T-LGLL. LGLL, large granular leukemia; TCR, T cell receptor. aOverall survival (OS) was defined as time from the diagnosis until death or last follow-up. Kaplan-Meier method was used for plotting Survival curves and log-rank test was used for comparison.

Supplementary Files

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- TLGLLsupplementtables1.docx