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Original Article

The non-leukemic T cell large granular lymphocytic leukemia variant with marked splenomegaly and neutropenia in the setting of rheumatoid arthritis - Felty syndrome and hepatosplenic T cell lymphoma mask

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Abstract: T cell large granular lymphocytic (T-LGL) leukemia is a rare type of mature T cell neoplasm. The typical features of T-LGL leukemia include an increased number of large granular lymphocytes in the peripheral blood, cytopenia (most commonly neutropenia), and mild-to-moderate splenomegaly. Up to 28% of patients with T-LGL leukemia have rheumatoid arthritis (RA). This study reports ten atypical cases (seven women and three men, median age 60.5 years) of RA-associated T-LGL leukemia presenting with lymphopenia, severe neutropenia, and marked splenomegaly. The weight of the spleens ranged from 892 to 2100 g (median 1100 g). Bone marrow histology and differential counts of bone marrow aspirates revealed no peculiarities in nine of ten cases. The red pulp of the spleen was expanded and showed moderate to strong infiltration by medium-sized slightly pleomorphic lymphocytes in nine cases and subtle infiltration in one. Although lymphocytic infiltration involved both cords and sinusoids, it was more apparent within the splenic cords. The white pulp was preserved and contained prominent germinal centers in eight patients and was atrophic in two patients. Immunohistochemically, malignant lymphocytes were CD3+, CD43+, and CD4- in all cases and TIA-1+ in nine out of ten. TCRαβ positivity and TCRγδ positivity was observed in six and four cases out of ten, respectively. All ten patients had T cell clonality in the spleen tissue, but in three cases it was absent in both blood and bone marrow. STAT3 mutations in the spleen tissue were detected in three of ten cases. In all eight cases studied, neither isochromosome 7q nor trisomy 8 was detected in the spleen tissue. Cases of RA-associated T-LGL leukemia with low LGL count in the peripheral blood, neutropenia, and marked splenomegaly present a diagnostic challenge and can be misdiagnosed as Felty's syndrome or hepatosplenic T cell lymphoma.

Keywords: Large granular lymphocyte leukemia, rheumatoid arthritis, Felty's syndrome, aleukemic leukemia, atypical, splenomegaly, neutropenia

Introduction

T cell large granular lymphocytic (T-LGL) leukemia is a rare mature T cell neoplasm with an indolent clinical course in most cases. Typical features of T-LGL leukemia include an increase in the number of peripheral blood large granular lymphocytes (LGLs), cytopenia, and splenomegaly without lymphadenopathy. Historically, a definitive diagnosis of T-LGL leukemia required an increase in the number of LGLs in the peripheral blood greater than 2×10^9/L for over 6 months, without an identified cause [1-3]. The most common cytopenia associated with T-LGL leukemia is neutropenia, which is found in about 84% of patients [4]. The splenic enlargement, most often from mild to moderate, was reported at a 19-50% frequency [5-8]. A peculiar feature of T-LGL leukemia is its association with autoimmune disorders. Rheumatoid arthritis (RA) occurs in 17-28% of the patients with T-LGL leukemia (RA-associated T-LGL leukemia) [4, 7].

The updated criteria allow for the diagnosis of T-LGL leukemia when the LGL count is less than 2×10^9/L and without the 6-month waiting period, provided that a clonal T cell population is

found in a patient with autoimmune diseases or cytopenia [6, 7, 9-12]. However, cases of T-LGL leukemia with a low LGL count (a non-leukemic variant of T-LGL leukemia) and marked splenomegaly present a diagnostic challenge. Such cases of T-LGL leukemia in patients with RA require differential diagnosis with Felty's syndrome (FS) and hepatosplenic T cell lymphoma (HSTCL) in the RA setting.

FS is an uncommon subset of RA complicated by neutropenia and, usually, splenomegaly. Cases of RA-associated T-LGL leukemia without absolute lymphocytosis in the peripheral blood and with concomitant neutropenia are clinically indistinguishable from FS and may be overlooked by clinicians due to misinterpretation of neutropenia and splenomegaly as FS. RA-associated T-LGL leukemia and FS are distinguished in clinical practice via the evaluation of T cell receptor (TCR) gene rearrangement. The monoclonal rearrangements of TCR genes (T cell clonality) are present in T-LGL leukemia but not in FS [13-15].

Clinically aggressive HSTCL, unlike T-LGL leukemia, is not associated with RA, and there are only occasional descriptions of the development of HSTCL in the setting of RA [16, 17]. However, immunosuppressive drugs and tumor necrosis factor inhibitors used in RA therapy, as well as chronic antigenic stimulation, may pose a risk for HSTCL development [17, 18]. Patients with HSTCL typically present with constitutional symptoms, massive splenomegaly without lymphadenopathy, and cytopenia, whereas peripheral blood involvement is uncommon [19]. Although, unlike T-LGL leukemia, patients with HSTCL usually manifest thrombocytopenia, neutropenia also occurs in 36-85% of cases [20].

In this study, we report ten atypical cases of a non-leukemic variant of RA-associated T-LGL leukemia with marked splenomegaly and severe neutropenia, which were initially misdiagnosed as FS or HSTCL. We also present the results of the morphological and molecular examination of the bone marrow and spleen in these cases and discuss the differential diagnosis with FS and HSTCL.

Materials and methods

We searched the V.A. Nasonova Research Institute of Rheumatology (Moscow, Russia) database from December 2010 until December 2020 for patients with RA that underwent splenectomy as a therapeutic or diagnostic option. Inclusion criteria were as follows: Over 18 years of age; RA diagnosis established according to the 2010 American College of Rheumatology/European League against Rheumatism criteria [21]; detection of T cell clonality in the spleen tissue. The exclusion criterion was the detection of B-cell clonality in the spleen tissue. The study protocol was approved by V.A. Nasonova Research Institute of Rheumatology (Moscow, Russia) Ethics Committee (№ 20/2020). This retrospective study included ten patients.

Peripheral blood and bone marrow aspiration smear specimens were available in three cases and ten cases, respectively. The tissue specimens of the spleen and bone marrow trephine biopsy were available in ten cases and seven cases, respectively. Data of eligible patients were retrieved from admitted medical charts and included the patient's age at the time of splenectomy, sex, blood tests before and after splenectomy, results of imaging studies, as well as the size and weight of the spleen.

Immunohistochemical studies of the spleen and bone marrow were carried out using the formalin-fixed paraffin-embedded (FFPE) tissue. The following antibodies were used at the dilutions suggested by the manufacturers: CD3 (polyclonal, Dako, Carpinteria, CA), CD4 (clone 4B12, Dako), CD8 (clone C8/144B, Dako), CD16 (clone 2H7, Novocastra Laboratories, Newcastle upon Tyne, UK), CD20 (clone L26, Dako), CD43 (clone DF-T1, Dako), T cell restricted intracellular antigen 1 (TIA-1) (clone 2G9, Immunotech, France), granzyme B (clone GrB-7, Dako), TCR-beta F1 (clone 8A3, Thermo Scientific, Waltham, MA), TCR-gamma (clone γ3.20, Thermo Scientific). After dewaxing and heat-induced antigen retrieval, immunostaining was performed using an Autostainer Link 48 (Dako, Denmark) according to the manufacturer's instructions. All immunostained samples were counter-stained with hematoxylin.

T cell clonality was examined using genomic DNA extracted from blood, bone marrow, and spleen tissue samples. T cell clonality was evaluated via rearranged TCR gamma (Vγ-Jγ), TCR-beta (Vβ-Jβ, Dβ-Jβ), and TCR delta (Vδ-Dδ-Jδ) gene amplification according to the BIOMED-2 standardized protocol [22]. Polymerase chain reaction (PCR) was carried out using an automated DNA Engine thermocycler (BioRad, Hercules, USA), and fragments were detected us-

ing an ABI PRISM 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA); the data were analyzed using GeneMapper software version 4.0 (Applied Biosystems, Foster City, CA).

Signal transducer and activator of transcription 3 gene (STAT3) mutations were examined using genomic DNA extracted from spleen tissue samples. Allele-specific TaqMan Real-Time PCR assays were used to determine the somatic point mutations p.Y640F, p.N647I, p.D661V, p.D661Y, p.D661H, and p.D661N in the STAT3 gene as described earlier [23].

FISH analysis for the detection of isochromosome 7q (iso(7q)) and trisomy of chromosome 8 was performed on FFPE tissue sections of the spleen using D7S522/CEP7 dual-color probes and a CEP8 probe (Abbott Molecular/Vysis, Downers Grove, IL, USA), respectively. A total of 200 interphase nuclei for each probe were analyzed.

Results

Clinical characteristics of patients, blood examination and results of splenectomy

Clinical characteristics and results of blood and bone marrow of ten patients are presented in **Table 1**. The patients were Caucasian, predominantly female (female/male ratio: 2.3:1), with a median age of 60.5 years (range, 42-77 years) at the time of splenectomy. The median time from the first detection of splenomegaly to splenectomy was 14.5 months (range, 2-144 months). All patients had marked splenomegaly without lymphadenopathy. The median white blood cell count before splenectomy was 1.2×10^9/L (range, 0.7-1.4×10^9/L). Neutropenia (<0.5×10^9/L) was detected in all cases; the median absolute neutrophil count was 0.136×10^9/L (range, 0.058-0.444×10^9/L). Absolute lymphocytopenia (lymphocyte count <1.0×10^9/L) was detected in all cases, which indicated that the number of LGLs in the peripheral blood was less than 1.0×10^9/L. In three cases (cases 1, 2, and 6) LGL count was less than 0.4×10^9/L. Monocytopenia (<0.2×10^9/L) was detected in six patients. The median hemoglobin level was 11 g/dL (range, 8.5-13.6 g/dL); eight patients had a hemoglobin level of <12 g/dL. The median platelet count was 116×10^9/L (range, 87-225×10^9/L); mild and moderate thrombocytopenia was detected in eight cases.

Splenectomy resulted in the improvement of the neutrophil count in six out of nine patients. The median absolute neutrophil count after splenectomy was 3.07×10^9/L (range, 0.17-9.145×10^9/L). Two patients were diagnosed with LGL lymphocytosis 1 year and 7 years after splenectomy.

Bone marrow examination

Bone marrow histology and differential counts of bone marrow aspirates revealed no peculiarities in nine of ten cases (**Table 1**). Only one patient (case 5) had an increase in the number of lymphocytes in the bone marrow (up to 62.6%) and interstitial lymphoid infiltration. All cases showed a decrease in granulocyte precursor and no signs of myelodysplasia. Immunohistochemical studies of bone marrow biopsy specimens showed a slight increase in the number of CD8-positive T cells in five patients (cases 2, 4, 7, 9, and 10) and interstitial/intra-sinusoidal infiltration by cytotoxic T-lymphocytes in two patients (cases 5 and 6).

Morphological examination of the spleen

The results of the spleen examination of patients are summarized in **Table 2**. The weight of the spleens ranged from 892 to 2100 g (median 1100 g). The red pulp was expanded and showed moderate to strong infiltration by medium-sized slightly pleomorphic lymphocytes in nine cases and subtle infiltration in one. Although lymphocytic infiltration involved both cords and sinusoids, it was more apparent within the splenic cords (**Figure 1**). Concomitant plasmacytosis was occasionally observed in the red pulp. The white pulp was preserved and contained prominent germinal centers in eight patients (**Figure 1**) and was atrophic in two patients (**Figure 2**). Immunohistochemical staining showed that malignant lymphocytes were CD3+, CD43+, and CD4- in all cases. Nine out of ten cases were TIA-1 positive, but granzyme B was absent in all cases. TCRαβ and TCRγδ positivity was observed in six and four cases, respectively. Malignant lymphocytes were CD8+ in all TCRαβ+ cases and one TCRγδ+ case.

T cell clonality, STAT3 gene mutations and FISH analysis

According to the selection criteria for the study, all ten patients had T cell clonality in the spleen tissue. In four TCRγδ+ cases, the clonal rearrangement of the TCRγ chain gene and biallelic clonal rearrangement of the TCRδ chain gene

Table 1. Splenectomy results and characteristics of ten patients with atypical RA-associated T-LGL leukemia

Case	Age (y)/ Sex	Blood just before splenectomy								Bone marrow before splenectomy			Blood after splenectomy		
		WBC ($\times10^9$/L)	Neutrophils ($\times10^9$/L)	Lymphocytes ($\times10^9$/L)	LGLs ($\times10^9$/L)	Monocytes ($\times10^9$/L)	Platelets ($\times10^9$/L)	Hb (g/dL)	TCR gene rearrangement	% of lymphocytes	IHC	TCR gene rearrangement	Neutrophils ($\times10^9$/L)	Lymphocytes ($\times10^9$/L)	LGLs ($\times10^9$/L)
1.	65/F	0.7	0.105	0.406	ND	0.189	107	10	ND	14.0	ND	Poly	3.07	3.380	ND
2.	52/F	1.2	0.084	0.876	0.312	0.24	114	12.3	Mono	10.4	Slight increase of CD8+ T cells	ND	9.145	4.185	ND
3.	60/F	1.2	0.084	0.912	ND	0.18	104	10.7	ND	13.2	ND	ND	0.999	9.879	4.060 (in 1 year)
4.	61/M	1.4	0.154	0.756	0.56	0.434	225	13.6	Poly	10.0	Slight increase of CD8+ T cells	Poly	0.17	2.480	ND
5.	50/F	1.21	0.145	0.908	ND	0.145	93	10	Mono	62.6	Interstitial infiltrate of CD8+ T cells	ND	1.705	31.372	28.737 (in 7 year)
6.	49/M	0.7	0.126	0.49	0.252	0.084	87	11.3	Poly	22.6	Interstitial/intra-sinusoidal infiltrate of CD8+ T cells	Poly	ND	ND	ND
7.	42/M	1.2	0.444	0.6	ND	0.132	164	11.2	Poly	7.8	Slight increase of CD8+ T cells	Mono	3.460	1.530	ND
8.	69/F	1.4	0.4	0.9	ND	0.1	118	11.7	ND	18.2	ND	ND	0.332	2.032	ND
9.	77/F	0.97	0.058	0.611	ND	0.3	132	10.7	ND	21.6	Slight increase of CD8+ T cells	Poly	3.780	2.079	ND
10.	71/F	1.1	0.176	0.55	ND	0.352	139	8.5	Poly	5.2	Slight increase of CD8+ T cells	Poly	6.155	2.247	ND

IHC, immunohistochemistry; WBC, white blood cell; y, years; +, positive/present; -, negative/absent; ND, no data; LGLs, large granular lymphocytes; TCR, T cell receptor; Mono, monoclonal TCR gene rearrangement; Poly, polyclonal TCR gene rearrangement.

Table 2. Spleen examination results of ten patients with atypical RA-associated T-LGL leukemia

Case	CD3	CD4	CD8	CD16	CD43	TIA-1	granzyme B	TCR	Extent of lymphoid infiltration of the red pulp	White pulp	TCR gene rearrangement			STAT3 gene mutation	Iso (7q)/ +8	size (mm)/mass (g)	time from first detected splenomegaly to splenectomy (mo)
											gamma	beta	delta				
1.	+	-	+	-	+	+	-	αβ	Moderate	Preserved with an prominent GCs	Mono	Mono	Poly	-	-/-	240×170×75/1950	22
2.	+	-	+	+	+	+ (low)	-	αβ	Subtle	Preserved with an prominent GCs	Poly	Mono	Poly	-	-/-	270×170×80/2100	66
3.	+	-	+	-	+	-	-	αβ	Moderate	Atrophic	Oligo	Mono	Poly	-	-/-	280×180/ND	144
4.	+	-	+	-	+	+	-	αβ	Moderate	Preserved with an prominent GCs	Mono	Mono	Poly	p.D661Y	-/-	215×150×55/892	8
5.	+	-	+	+	+	+	-	αβ	Moderate	Preserved with an prominent GCs	Mono	Mono	Poly	p.Y640F	-/-	230×160×90/1850	3
6.	+	-	+	+	+	+	-	αβ	Moderate	Atrophic with atretic follicles	Mono	ND	ND	-	ND	310×190×110/ND	139
7.	+	-	-	-	+	+	-	γδ	Moderate	Preserved with an prominent GCs	Mono	Poly	Mono (biallelic)	-	-/-	220×160×50/1100	12
8.	+	-	-	+	+	+	-	γδ	Moderate to strong	Preserved with an prominent GCs	Mono	Poly	Mono (biallelic)	-	-/-	190×120×65/900	12
9.	+	-	+	+	+	+	-	γδ	Moderate	Preserved with an prominent GCs	Mono	Mono	Mono (biallelic)	p.D661Y	ND	160×100×80/900	2
10.	+	-	-	+	+	+	-	γδ	Moderate to strong	Preserved with an prominent GCs	Mono	Mono	Mono (biallelic)	-	-/-	210×130×80/ND	17

GCs, germinal centers; TCR, T cell receptor; STAT3, signal transducer and activator of transcription 3 gene; mm, millimeters; g, grams; iso (7q), isochromosome 7q; +8, trisomy of chromosome 8; +, positive/present; -, negative/absent; ND, no data; mono, monoclonal rearrangement; poly, polyclonal rearrangement; oligo, oligoclonal rearrangement; mo, months.

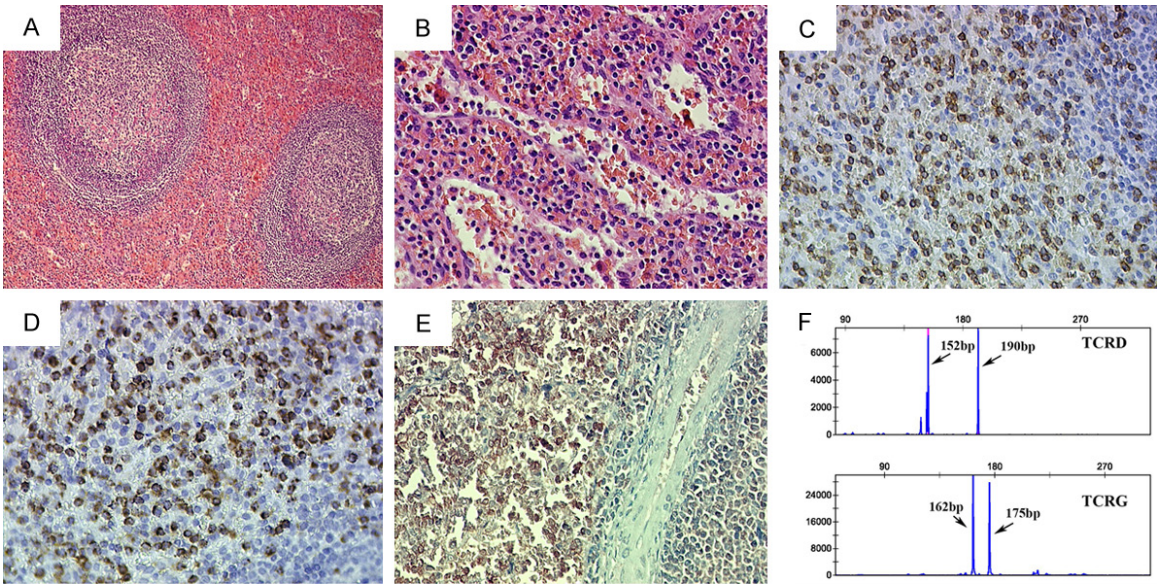

Figure 1. Case 8. (A) The spleen shows preserved white pulp with prominent germinal centers and lymphocytic infiltration of the red pulp (H&E, ×100). (B) Medium-sized slightly pleomorphic lymphocytes infiltrate both cords and sinusoids, but more marked within the splenic cords (H&E, ×400). (C-E) Immunohistochemistry shows that the atypical population in the red pulp was positive for CD3 (C, ×400), TIA-1 (D, ×400), and TCRγδ (E, ×400). (F) T cell receptor gamma (TCRG) and delta (TCRD) clonality analysis of spleen sample shows biallelic clonal rearrangement.

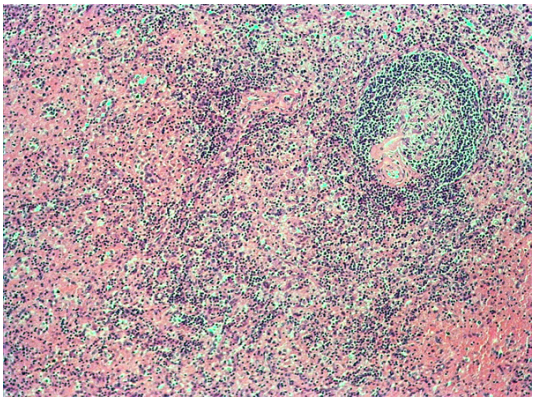

Figure 2. Histological examination of the spleen from case 6 demonstrates atrophic white pulp with atretic follicles and infiltration of the red pulp cords and sinusoids with lymphoid cells (H&E, ×100).

were detected. Two of these patients also showed clonal rearrangement of the TCRβ chain gene. In one of the six TCRαβ+ cases, the determination of the T cell clonality was based only on the detection of the TCRγ chain gene clonal rearrangement. In the other five TCRαβ+ cases, a clonal rearrangement of the TCRβ chain gene and polyclonal rearrangement of the TCRδ gene was detected. Three of these five TCRαβ+ cases showed a clonal rearrangement of the TCRγ chain gene, and in two cases the rearrangement of the TCRγ chain gene was poly/oligoclonal.

Of the eight cases where blood and/or bone marrow was available, T cell clonality was detected in three cases. Of the remaining five cases, three cases showed absent T cell clonality in both blood and bone marrow, and two showed absent T cell clonality in bone marrow (blood was unavailable in these cases).

STAT3 mutations in the spleen tissue were detected in three of ten cases. The p.D661Y mutation was detected in two cases and p.Y640F mutation in one. In all eight cases studied, neither iso (7q) nor trisomy of chromosome 8 was detected in the spleen tissue.

Discussion

Dominant clinical features in all our patients included severe neutropenia and marked splenomegaly without lymphadenopathy that developed in the presence of RA. This clinical picture and non-leukemic blood (all patients had lymphopenia) initially led to misinterpretation of these cases as FS or spleen lymphoma. In the literature, we could find only two cases of T-LGL

leukemia in the setting of RA, which manifested with lymphopenia and neutropenia in the peripheral blood [24, 25]. In one of these cases, the spleen was not enlarged, and in the other case mild splenomegaly was found. In both cases, bone marrow examination resulted in the diagnosis of T-LGL leukemia. In all but one of our cases, bone marrow histology and differential counts of bone marrow aspirates were insufficient for the diagnosis of T-LGL leukemia and T cell clonality in the bone marrow was detected in only one of the six cases studied. Immunohistochemistry studies of the bone marrow using CD8 can detect interstitially distributed clusters and linear arrays of intravascular CD8+ T cells in up to 83% of the patients with T-LGL leukemia [26]. However, most of our patients showed only a slight increase in the number of CD8+ T cells in the bone marrow, which can also be observed in RA patients without T-LGL leukemia [27-29].

Limited data are available in the literature on the pathology of the spleen in T cell LGL leukemia because the spleen is rarely removed for initial pathological diagnosis. The pattern of splenic involvement by T-LGL leukemia in eight of ten patients in our study showed a preserved white pulp with prominent germinal centers and enlargement of the red pulp because of infiltration by small lymphoid cells in the sinuses and more marked within pulp cords and was similar to spleen histology previously described by other authors in this disease [30-32].

It can be difficult to distinguish splenic involvement in T-LGL leukemia from that in FS. It should be noted that, to the best of our knowledge, studies on spleen morphology in FS have not evaluated the clonality of T cells, and the diagnosis of FS was performed based on clinical data. In patients with FS, the spleen shows non-specific findings, such as germinal center hyperplasia, plasmacytosis, and enlarged sinuses and pulp cords [33-35]. According to Agnarsson et al., patients with FS lack lymphoid infiltration of the red pulp [30]. However, in some cases of T-LGL leukemia, the neoplastic infiltrate in the red pulp may be subtle, which complicates the diagnosis [36]. In one of our patients (case 2), the histological and immunohistochemical examination of the bulky spleen also revealed only a minimal increase in the number of cytotoxic T cells in the red pulp, which was not enough to suspect spleen involvement by T-LGL leukemia.

Detection of monoclonal rearrangements of the TCR genes is essential to distinguish T-LGL leukemia from FS. However, in cases with low tumor burden, the assessment of T cell clonality can be challenging. Examination of blood and bone marrow did not reveal T cell clonality in both blood and bone marrow in three of our cases. In these cases, verifying the diagnosis of T-LGL leukemia was only possible via spleen examination. In addition, there is a considerable discussion regarding the significance of dominant T cell clones as a hallmark of T cell malignancy because small populations of clonally expanded T-LGLs are observed both in healthy individuals and in exuberant reactive responses [37-42]. There were two cases in our files that we classified as FS because we did not detect T cell clonality. In one of them, the lymphoid infiltration of the red pulp was subtle, while in the other, we did not observe any morphological and immunohistochemical features to differentiate this case from splenic involvement by T-LGL leukemia.

The diffuse involvement of the red pulp by monotonous population cytotoxic T cells necessitates differential diagnosis between splenic involvement by T-LGL leukemia and HSTCL. Histologically, unlike splenic involvement by T-LGL leukemia, predominant intra-sinusoidal infiltration of the red pulp and atrophy (or loss) of the white pulp are typically observed in HSTCL [30-32, 36]. However, these morphological features are not entirely reliable. Spleen samples with HSTCL may show preserved residual islands of normal white pulp [43, 44] and evaluation of the degree of lymphoid infiltration in the sinuses and pulp cords is quite subjective. In two of our T-LGL leukemia cases, the white pulp was atrophied and the morphological appearance of the spleen was indistinguishable from that of HSTCL. We believe that white pulp atrophy may be due to the duration of the disease rather than spleen size.

Immunophenotypic features of HSTCL overlap with those of T-LGL leukemia and the differential diagnosis of T-LGL leukemia versus HSTCL can be particularly problematic in cases of γδT-LGL leukemia. Although it is accepted that in contrast to T-LGL leukemia, the malignant cells of HSTCL have a non-activated cytotoxic pheno-

type (TIA-1+, granzyme B-) [20, 45], a literature review by Yabe et al. showed that up to 41% of HSTCL cases are granzyme B positive [19]. Intriguingly and inexplicably, immunohistochemical examination revealed no expression of granzyme B in any of our cases of spleen involvement by T-LGL leukemia.

FISH analysis for iso (7q) is important for the differential diagnosis of HSTCL and T-LGL leukemia. Iso (7q) has been reported in approximately 69% of HSTCL cases [44, 46], but never in T-LGL leukemia cases. Trisomy 8 is observed in up to 53% of HSTCL cases [44], but, as far as we know, it has been described in only two patients with T-LGL leukemia [47, 48]. FISH analysis of spleen tissues was negative for iso (7q) and trisomy 8 in all eight cases in our series. Activating somatic mutations in *STAT3* were identified in 27-72% of T-LGL leukemia cases [49-52]. *STAT3* mutations were detected in the spleen tissue of 30% of the patients in our cohort. However, unlike iso (7q) and trisomy 8, the diagnostic value of *STAT3* mutations in the differential diagnosis of HSTCL and T-LGL leukemia seems to be less significant, since *STAT3* mutations have been identified in 9% of HSTCL cases [53].

In addition, several clinical features may help with the differential diagnosis of T-LGL leukemia and HSTCL. HSTCL affects predominantly men with a median age of about 34 years [20]. In our cohort, the median age was significantly higher (60.5 years) and strong female predominance was observed. The course of the disease in our patients was indolent. None of the patients had received chemotherapy before splenectomy, and to our knowledge, there have been no deaths from T-LGL leukemia progression.

The terminal effector memory phenotype of T-LGL leukemic cells suggests an antigen-driven mechanism of tumor development. However, the site of T-LGL leukemic cells production is unknown. The predominant localization of tumor lymphocytes in the spleen with the development of bulky splenomegaly in our cohort suggests that neoplastic lymphoid proliferation occurred predominantly in the spleen and/or tumor cells had affinity for the spleen tissue. All of our patients had RA according to the selection criteria, and it is unclear whether T-LGL leukemia with non-leukemic blood picture and massive splenomegaly can occur in patients without RA.

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Disclosure of conflict of interest

None.

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