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CASE REPORT

Three Cases of Large Granular Lymphocytic Proliferations Detected During Health Screening

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ABSTRACT

Background: **Large granular lymphocytic leukemia (LGLL) is an indolent, often asymptomatic neoplasm easily overlooked in routine screening. Morphology and flow cytometry aid early diagnosis via markers TRBC1, CD57 and CD159a.**
Case Presentation: **Three screening-detected asymptomatic LGLL patients were enrolled: $CD4^+$ T-LGLL (high CD57), $CD8^+$ T-LGLL and rare CLPD-NK. Sustained clonality was confirmed at follow-up, with all placed on regular surveillance.**
Conclusions: **Combined blood morphology and flow cytometry facilitates early LGLL identification. TRBC1/ CD159a verify clonality, and asymptomatic patients require long-term monitoring.**
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KEYWORDS

large granular lymphocytic leukemia, physical examination screening, peripheral blood cell morphology, flow cytometry

LIST OF ABBREVIATIONS

LGLL - Large Granular Lymphocytic Leukemia
CLPD-NK - Chronic Lymphoproliferative Disorder of NK cells
NK-LGLL - NK Large Granular Lymphocytic Leukemia
ANKL - Aggressive NK-cell Leukemia
WHO - World Health Organization
QC - Quality Control
LY - Lymphocyte
TRBC1 - T Cell Receptor Beta Constant Region 1
AI - Artificial Intelligence
CBC - Complete Blood Count

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INTRODUCTION

Large granular lymphocytic leukemia (LGLL) is a rare chronic lymphoproliferative neoplasm defined by clonal expansion of large granular lymphocytes, accounting for 2% - 5% of all lymphoproliferative malignancies [1, 2]. Neoplastic lymphocytes contain abundant azurophilic cytoplasmic granules and display characteristic T-cell or NK-cell immunophenotypes. According to the 2017 WHO classification, LGLL comprises three subtypes: T-LGLL, chronic lymphoproliferative disorder of NK cells (CLPD-NK) and aggressive NK-cell leukemia (ANKL) [3,4]. In the 5th edition of the 2022 WHO classification, CLPD-NK was renamed NK-LGLL [5].

The 2022 WHO diagnostic criteria require persistent peripheral blood large granular lymphocyte counts ≥ 0.5 x 10^9/L for at least six months. Nevertheless, patients below this threshold may also receive a diagnosis supported by clinical manifestations, bone marrow infiltration, typical immunophenotypic and molecular abnormalities [6].

CASE PRESENTATION

Ethics approval and patient consent

This study was approved by the Ethics Committee of Aerospace Center Hospital (Approval No.: 2023 (122), Date: 08-10-2023) and conducted in accordance with the Declaration of Helsinki. All three patients were contacted and provided signed informed consent to publish their de-identified test data, and they agreed to supply external hospital test records for data analysis.

Detection methods

Routine blood analysis and Wright-Giemsa smears were tested on BC-6800Plus with QC; AI morphological screening used Mindray MC-80 (V1.2.1). For flow cytometry, 2 mL EDTA blood was stained with BD antibodies (1:20 dilution, 4℃, 30 minutes dark incubation). We acquired ≥ 100,000 lymphocyte events on BD FACSAria Fusion with standardized gating and batch compensation, using markers for T-LGLL and CLPD-NK.

Clinical characteristics

All three patients remained asymptomatic at initial screening and follow-up. No underlying diseases, relevant family history or recent medication were reported. Physical examination revealed no lymphadenopathy, splenomegaly or other abnormal signs. DNA testing for common respiratory pathogens was performed to exclude infectious interference, and all results were negative. Laboratory findings of the patients are detailed in Table 1 and Figure 1.

Patient 1 ($CD4^+CD8^-$ T-LGLL):

A 65-year-old male received routine health screening on July 5, 2022. Routine blood tests showed no remarkable abnormalities, whereas peripheral blood morphology revealed large granular lymphocytes accounting for more than 50% of total lymphocytes. Flow cytometry confirmed clonal proliferation of mature $CD4^+$ T cells with TRBC1 (T Cell Receptor Beta Constant Region 1) monotypia and high CD57 expression. Persistent clonal abnormality was verified at the 6-month follow-up, and the diagnosis of T-LGLL was established. As a non-local resident, he was recommended to undergo regular surveillance at local hospitals and seek prompt medical attention in case of fever, fatigue or bleeding.

Patient 2 ($CD4^-CD8^+$ T-LGLL):

A 55-year-old male presented for health screening on March 12, 2024 with marked lymphocytosis. Peripheral blood smear showed large granular lymphocytes constituted more than 50% of lymphocytes, and flow cytometry demonstrated clonal proliferation of mature $CD8^+$ T cells. Retrospective laboratory data revealed an overall upward trend in lymphocyte counts over the past 8 years; transient declines in 2016 and 2020 were presumed secondary to bacterial infection. Persistent clonal abnormalities were confirmed at the 6-month follow-up, consistent with T-LGLL diagnosis. Despite the absence of current symptoms, progressive elevation of lymphocytes remained a potential risk. The patient was instructed to receive CBC testing every six months and seek prompt medical attention for fatigue, recurrent infections or bleeding, and he agreed to follow the monitoring plan (Table 2).

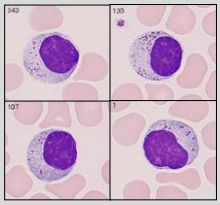
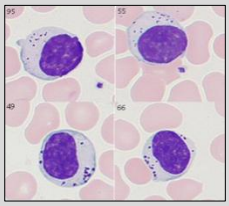
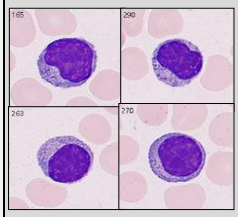
Patient 3 (CLPD-NK):

An 81-year-old female received health screening on August 12, 2022 and presented with significant lymphocytosis. Peripheral blood morphological analysis showed large granular lymphocytes exceeded 50% of lymphocytes, and flow cytometry identified clonal NK-cell proliferation. According to the patient and her family, elevated lymphocytes had persisted for nearly 10 years, yet further evaluation was delayed due to advanced age and lack of symptoms. Follow-up testing in May 2024 confirmed sustained clonal NK-cell expansion, and CLPD-NK was diagnosed. Long-term abnormal hematological results caused mild anxiety. After counseling on disease epidemiology and natural history, her concerns were relieved, and she agreed to annual follow-up.

DISCUSSION

Indolent LGLL subtypes pursue an insidious course. Patients may remain asymptomatic with persistent lymphocytosis, which is prone to missed diagnosis in routine screening. Flow cytometric lymphocyte subtyping is costly and unsuitable for population-wide screening. A peripheral blood large granular lymphocyte proportion > 50% serves as a valuable early marker; routine blood tests combined with manual morphological review constitute an efficient initial screening approach

Table 1. Laboratory data of three patients at initial screening and follow-up.

		Patient 1 ($CD4^+CD8^-$ T-LGLL)		Patient 2 ($CD4^-CD8^+$ T-LGLL)		Patient 3 (CLPD-NK)	
Initial screening examination results	lymphocyte parameters in CBC	20220705	LY 3.69 x 10^9/L, LY 46.83%	20240312	LY 7.99 x 10^9/L, LY 66.86%	20220812	LY 13.18 x 10^9/L, LY 74.30%
	peripheral blood microscopy showed large granular lymphocytes constituted more than 50% of lymphocytes						
	flow cytometry results		T cells: 65.04% $CD4^+$ T cells: 80.07% CD3+CD57+cells: 66.98% $CD3^+TRBC1^+$ cells : 78.90%		T cells: 86.58% $CD8^+$ T cells: 73.14% CD3+CD57+cells: 86.27% $CD3^+TRBC1^+$ cells : 84.57%		NK cells: 66.30% $CD159a^+$ cells: 95.97%
Follow-up examination results	lymphocyte parameters in CBC	20230510	LY 3.71 x 10^9/L, LY 50.61%	20250511	LY 6.73 x 10^9/L, LY 65.83%	20240506	LY 8.28 x 10^9/L, LY 62.90%
	flow cytometry results		T cells: 68.02%, $CD4^+$ T cells4: 82.75% CD3+CD57+cells: 63.75% $CD3^+TRBC1^+$ cells : 80.41%		T cells: 87.89%, $CD8^+$ T cells: 70.12% CD3+CD57+cells: 85.13% $CD3^+TRBC1^+$ cells : 85.57%		NK cells: 78.49% $CD159a^+$ cells: 94.21%

Fasting EDTA-K2 whole blood (2 mL) was collected and mixed immediately. Slides were automatically prepared on the Mindray SC-120 with spreading parameters adjusted for hematocrit and viscosity, followed by methanol fixation, staining and drying. AI-assisted digital analysis was performed using the Mindray MC-80 morphology system (V1.2.1). Two hundred leukocytes in the distal one-third of smears were counted and preliminarily differentiated.

Table 2. Historical annual lymphocyte percentage results of patient 2.

	LY (x 10^9/L)	LY%
200904	2.73	47.12
201004	3.04	44.30
201104	2.70	45.90
201204	3.76	48.65
201304	3.30	49.90
201404	3.39	48.40
201504	3.51	48.84
201604	2.93	40.83
201704	3.92	49.62
201804	4.63	55.10
201904	4.61	51.71
202004	4.12	38.32
202104	4.63	57.64
202207	4.33	55.71
202304	4.19	56.97

LY: lymphocyte (normal 1.1 - 3.2 x 10^9/L), LY%: lymphocyte % (normal 20 - 50%).

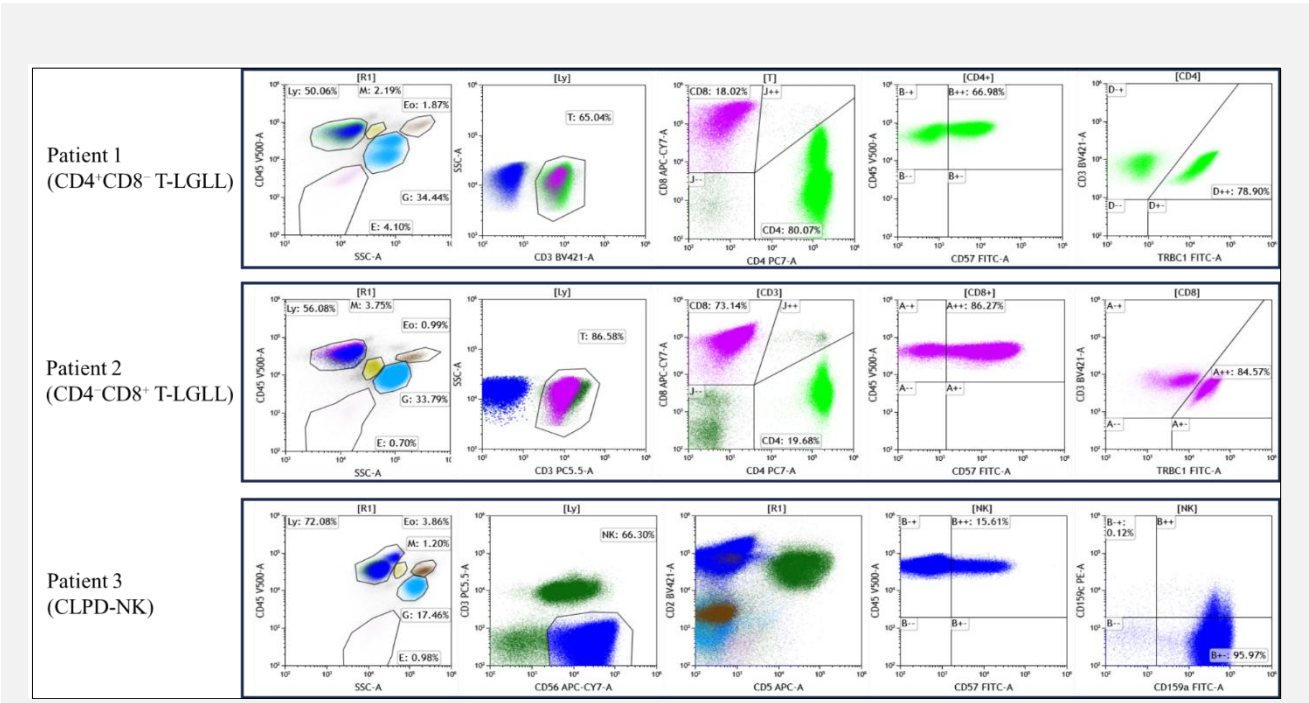


Figure 1. Flow cytometric findings of peripheral blood in three patients during initial screening.

for asymptomatic individuals. Automated slide stainers and AI morphology systems greatly reduce labor burden, yet they cannot distinguish large granular lymphocytes from small lymphocytes, necessitating manual microscopic verification.

This study enrolled three patients with chronic large granular lymphocytic proliferative disorders. Monoclonal proliferation was verified via biomarker detection: Cases 1 and 2 presented monoclonal T-cell expansion with TRBC1 expression exceeding 75% [7], while Case 3 showed monoclonal proliferation with 95.97% CD 159a-positive cells. The three cases involved distinct LGLL subtypes with unique immunophenotypic features. Case 1 was $CD4^+CD8^-$ T-LGLL, characterized by persistent peripheral $CD4^+$ T lymphocytosis and prominent CD57 expression [8,9], suggesting an atypical mixed lymphocyte phenotype. Case 2 was $CD4^-CD8^+$ T-LGLL, with dynamically monitored progressive early-stage lymphocytosis that intuitively reflected the early disease characteristics. Case 3 corresponded to the rare CLPD-NK subtype, which accounts for approximately 10% of all LGLL cases.

T-LGLL and NK-LGLL follow similar therapeutic strategies. Asymptomatic patients receive regular surveillance without pharmacotherapy. Immunosuppressants are administered to improve cytopenia when treatment is indicated. Widely accepted treatment criteria include: absolute neutrophil count < 0.5 x 10^9/L; absolute neutrophil count > 0.5 x 10^9/L with recurrent infections; severe anemia; severe thrombocytopenia; and concomitant serious complications [6]. The three patients are currently under regular follow-up. They were advised to attend hospital timely upon occurrence of the above conditions, and all agreed with this strategy.

CONCLUSION

This case series describes three subtypes of chronic large granular lymphocytic proliferative disorders. TRBC1 immunophenotyping and CD159a expression facilitate identification of clonal expansion. $CD4^+CD8^-$ T-LGLL exhibits prominent CD57 expression. All patients remain asymptomatic and receive regular surveillance. This study supplements immunophenotypic data of LGLL subtypes and supports the value of morphological combined with flow cytometric screening.

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Declaration of Generative AI in Scientific Writing:
All content in this article was independently written by the authors. No generative AI tools were used for content generation. All experimental data, case analyses and conclusions are authentic and reliable, complying with medical paper standards and academic integrity requirements.

Declaration of Interest:
The authors declare that they have no competing interests.

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