Clin. Lab. 2024;70:XXX-XXX

CASE REPORT

A Rare Case of NK Large Granular Lymphocytic Proliferative Disorder

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SUMMARY

Background: **Chronic NK-cell lymphoproliferative disease (CLPD-NK) is a very rare lymphoproliferative disorder in which patients often have an elevated lymphocyte population without clinical symptoms.**
Methods: **In this particular case, a middle-aged woman presented with a consistent elevation in her lymphocyte proportion over a span of four consecutive years during physical examinations, without manifesting any other notable clinical symptoms. The underlying cause of this phenomenon was ultimately identified through a comprehensive evaluation that encompassed peripheral blood cell morphology analysis, lymphocyte subset profiling, and peripheral blood immunophenotyping. These diagnostic tools collectively provided crucial insights into the nature of the disease.**
Results: **The patient was finally diagnosed with CLPD-NK. As part of her management plan, the patient was advised to undergo regular annual physical examinations to monitor the progression of the disease and any potential changes in her health status.**
Conclusions: **CLPD-NK is a chronic progressive lymphoproliferative disease, which can be followed up regularly if there are no clinical symptoms. Severe reductions in neutrophils, red blood cells, and platelets or other complications may require chemotherapy or bone marrow transplantation.**
(Clin. Lab. 2024;70:xx-xx. DOI: 10.7754/Clin.Lab.2024.240712)

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Case Report accepted July 12, 2024

KEYWORDS

chronic NK-cell lymphoproliferative disease, large granular lymphocytic leukemia

INTRODUCTION

Large granular lymphocytic leukemia (LGLL) is a rare clonal proliferation disorder of cytotoxic T lymphocytes (CTL) and natural killer (NK) cells, which can be further classified into chronic NK cell lymphoproliferative disorder (CLPD-NK) and aggressive NK cell leukemia (ANKL) based on the disease course. Among these, CTL-LGLL is the most prevalent form, accounting for approximately 85% of all LGLL cases, where CLPD-NK is the rarest, comprising less than 10% of the total. Given its exceedingly low incidence and the wide array of clinical presentations it can manifest, CLPD-NK remains a poorly understood condition. This lack of un-

Table 1. Results of regular blood test.

Date	WBC	NE	NE%	LY	LY%	RBC	HGB	PLT
20200916	5.53 N	2.37 N	42.9 N	2.57 N	46.50 N	4.31 N	140 N	232 N
20211029	5.10 N	1.76↓	34.5↓	2.69 N	52.80↑	4.28 N	142 N	231 N
20220722	6.13 N	1.56↓	25.4↓	4.05↑	66.10↑	4.35 N	141 N	230 N
20230807	8.15 N	1.82↓	22.3↓	5.68↑	69.70↑	4.38 N	143 N	226 N

WBC - white blood cell (normal 3.5 - 9.5 x 10^9/L), NE - neutrophil (normal 1.8 - 6.3 x 10^9/L), NE% - neutrophil% (normal 40 - 75%), LY - lymphocyte (normal 1.1 - 3.2 x 10^9/L). LY% - lymphocyte % (normal 20 - 50%), RBC - red blood cell (normal 3.8 - 5.1 x 10^{12}/L), HGB - hemoglobin (normal 115 - 150 g/L), PLT - platelet (normal 125 - 350 x 10^9/L), ↑ - Higher than the reference interval, ↓ - Lower than the reference interval, N - normal.

Table 2. EB virus antibody.

Test	Result	Unit	Reference scope
EB virus capsid IgM	1.14	U/mL	0 - 40
EB virus capsid IgG	> 750	U/mL	0 - 20
EB virus capsid IgA	0.19	COI	0 - 1.1
EB virus core IgG	426	U/mL	0 - 20
EB virus core IgA	0.25	COI	0 - 1.1
EB virus early IgM	0.23	COI	0 - 1.1

The detection values for both EB virus capsid IgG and EB virus core IgG are above the normal range, suggesting that the patient has had a previous infection with the EB virus.

Table 3. Lymphocyte subpopulation.

Test	Result	Unit	Reference scope
T cell%	26.19	%	56 - 86
CD4+T cell%	14.53	%	33 - 58
CD8+T cell%	10.31	%	13 - 39
B cell%	9.29	%	5 - 22
NK cell%	64.67	%	5 - 26
CD4+T cell/CD8+T cell	1.41	/	0.71 - 2.78
Absolute value of lymphocytes	4836	/μL	1,530 - 3,700
Absolute value of NK cells	3191	/μL	84 - 724

The proportion and absolute count of NK cells significantly exceed the reference range, suggesting abnormal NK cell proliferation in the patient's body.

derstanding often leads to diagnostic challenges, resulting in misdiagnoses and the unnecessary utilization of healthcare resources. As such, there is a pressing need for further research and education on CLPD-NK to improve diagnostic accuracy [1].

CASE PRESENTATION

A 55-year-old female patient underwent routine health check-ups at our hospital from 2020 to 2023, during which the proportion of lymphocytes progressively increased (Table 1). To confirm the diagnosis, additional tests including EB virus antibody panel, peripheral blood smear, lymphocyte subpopulation classification, and peripheral blood flow cytometry were performed in

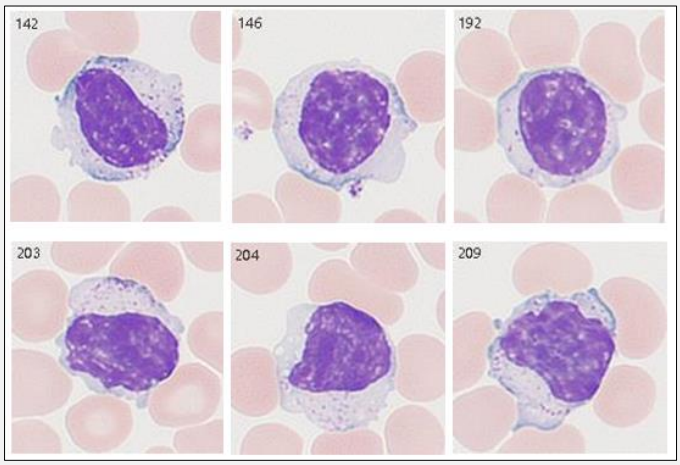

Figure 1. Peripheral blood smears (The patient's peripheral blood smear contains a large amount of lymphocytes rich in particles).

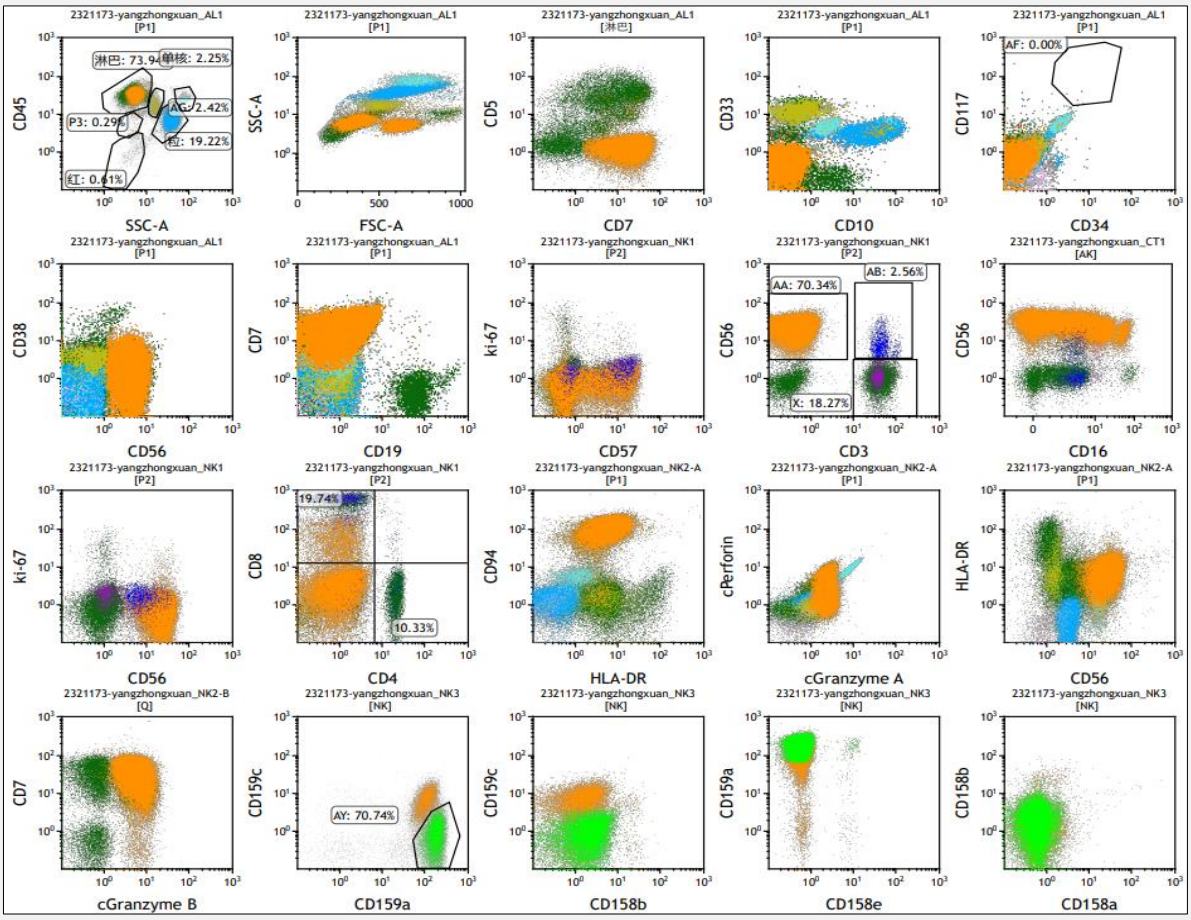

Figure 2. Peripheral blood immunophenotype.

August 2023.

The peripheral blood smear revealed an increase in large granular lymphocytes (Figure 1). Lymphocyte subpopulation analysis showed that CD16+CD56+ NK cells accounted for 64.67% of all lymphocytes (Table 3). The flow cytometry results of peripheral blood cells showed that lymphocytes (Figure 2) accounted for 73.94%, of which CD3+CD56-T cells accounted for 18.27%, CD4+/CD8+ accounted for 1.34, and CD3-CD56+NK cells accounted for 70.34%. Most lymphocytes express CD7, CD94, Granzyme B, CD159a. Some lymphocytes express CD57, CD16, cPerforin, and CD-159c. This patient's lymphocytes almost do not express CD5, CD33, CD10, CD19, CD34, CD117, CD38, ki-67, CD4, CD8, HLA DR, Granzyme A, CD158b, CD158, and CD158e. NK cell phenotype is abnormal. EB virus antibody testing (Table 2) suggests that our patient has been infected with EB virus before.

Given the patient's progressively increasing lymphocyte proportion over four consecutive years, the presence of morphologically similar large granular lymphocytes on the peripheral blood smear and the increased NK cell population on immunophenotyping, a diagnosis of CLPD-NK was made. The patient underwent a reexamination of peripheral blood related tests six months later, and the results were similar to this one. The patient was advised to undergo regular check-ups and seek medical attention if any discomfort arises.

DISCUSSION

CLPD-NK is an extremely rare lymphoproliferative disease, in which patients only experience lymphocyte proliferation in the early stages without clinical symptoms, often detected during physical examinations. At present, China has not yet developed a CLPD-NK disease guideline. In clinical practice, Tanahashi T et al. recommended a simplified method for diagnosing LGLL, which simultaneously meets the following two criteria: lymphocyte proportion > 52%, LGL proportion > 50% lymphocytes [2]. Drillet G et al. proposed a scoring mechanism for diagnosing CLPD-NK, such as NK cell count > 1 G/L; KIR restricted phenotype; CD94/NKG2A high expression; *STAT3*, *STAT5b*, *TET2*, *TNFAIP3*, *CCL22* mutations [3]. This case meets the diagnostic criteria mentioned in these two articles.

This case suggests that when the proportion of peripheral blood cells is abnormal, we should recheck the morphology of peripheral blood cells and add peripheral blood flow cytometry items. At present, the etiology of this disease is not fully understood. Some studies suggest that the imbalance of cell apoptosis dynamics leads to the sustained survival of LGL, which is related to various activation pathways (JAK-STAT, TET2, Ras) and inhibitory proteins (S1P, FLIP, SERPINB9) [4-6]. Further research is needed on the effects of various viral infections on these genes, such as the EB virus.

T-LGLL and CLPD-NK are more common in elderly patients [7,8], with slow progression and a median survival of 9 - 10 years. The treatment methods for both are almost the same, with no clinical symptoms and no need for treatment. The use of immunosuppressants is mainly used to correct cytopenia. Treatment indications include: neutrophil absolute value < 0.5 x 10^9/L; neutrophil absolute value > 0.5 x 10^9/L but accompanied by recurrent infections, severe anemia, severe thrombocytopenia, and other serious complications. On the contrary, ANKL is a highly malignant disease with a median age of 39 years at diagnosis and a median survival time of less than 2 months. Due to the rarity of related cases, it is difficult to conduct large-scale clinical studies. Currently, most treatments are empirical, such as combination chemotherapy or stem cell transplantation [9].

CONCLUSION

This case report highlights an exceptionally rare instance of CLPD-NK, characterized by a progressive increase in lymphocyte proportion and a rise in the clonality of NK cells. Given the scarcity of such cases globally and the absence of standardized diagnostic and treatment protocols, patients with CLPD-NK are at high risk of being misdiagnosed or having their condition overlooked.

It is my hope that by sharing this case, we can contribute to the growing body of knowledge surrounding CLPD-NK and provide valuable insights for clinicians. By gathering and analyzing more relevant cases, we can develop a better understanding of the disease's clinical manifestations, diagnostic challenges, and potential treatment options. This, in turn, can help to improve diagnostic accuracy, inform treatment decisions, and ultimately enhance patient outcomes.

Declaration of Interest:

The authors declare that they have no conflict of interest.

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