Article published online: 2021-06-03

Letter to Editor

CD4+/CD8- T cell Large Granular Lymphocytic Leukemia: A rare Entity

Sir,

Large granular lymphocytic leukemia (LGL) is a well-recognized disorder of mature T-cells or NK cells. T-cell LGL leukemia (T-LGL) is characteristically a disorder of mature CD3+/CD8+ cytotoxic T-cells. Rare variants include CD 3+/CD4+/CD8-cases. To the best of our knowledge, 11 such cases (4 cases by Lima *et al*.[1] in 2003, 4 cases by Olteanu *et al*. in 2010,[2] 2 cases by Mutreja *et al*.[3] in 2014, and 1 case by Rabade *et al*.[4] in 2014) of T-LGL showing CD3+/CD4+/CD8-immunophenotype has been published in literature so far. There is a paucity of literature explaining the monoclonal expansion of CD3+/CD4+ T-LGL.[1] Unlike CD8+ T-LGL, CD4+ T-LGL does not show cytopenia, autoimmune phenotypes,[1,5] or splenomegaly. However, CD4+ T-LGL is frequently associated with nonhematological malignancies.[1] Here, we report a case presenting with CD3+/CD4+/CD8-immunophenotype. Such immunophenotypic variant form of T-LGL cases should have a close clinical follow-up as they are prone to develop either simultaneously or months and years after, secondary hematological or nonhematological malignancies.[1]

We received a peripheral blood sample for immunophenotyping from a 51-year-old female with a 4-month history of persistent lymphocytosis. Clinical examination revealed a single cervical lymphadenopathy with no hepatosplenomegaly. The complete blood count showed mild anemia (hemoglobin - 11.9 g/dL), a normal platelet count (platelets 150,000/μL), and absolute lymphocytosis (total leukocyte count 13.0 × 10^3/μL with 79.5% lymphocytes). Peripheral smear examination revealed a large number of large granular lymphocytes. Cytogenetic analysis was not performed.

Immunophenotyping of peripheral blood was carried out using the lyse wash method and a four-color flow cytometry panel [Table 1]. The antibody clones used are shown in Table 2. The sample was run on a BDFACS Calibur instrument (Becton/Dickinson Biosciences), and the immunophenotyping data were analyzed with BD Cell Quest software. The percentage of positive cells above a threshold set against a processed isotype control tube was used to express the florescence measurement. Flow cytometry analysis of a heparin peripheral blood sample showed a large lymphoid cell cluster (62% of total cells) with bright CD45 positivity. The cells showed positivity for CD3 (96%), CD4 (94%), CD5 (96%), CD2 (97%), CD16 (41%), CD56 (90%), and-CD57 (91%), indicating a T-cell origin [Figure 1]. There was an aberrant loss of CD7 expression, and CD8 expression was negative [Figure 1]. Other B lymphoid cells markers were negative including CD10, CD19, CD23, CD20, CD38, and surface

Table 1: Antibody clones (BD) used for flow cytometry

Marker	Clone	Fluorochrome	Expression (% +ve)
CD3	SK7	PE	9 6
CD4	RM4-5	APC	9 4
CD2	S5.2	FITC	9 7
CD5	L17F12	FITC	9 6
CD7	M-T701	PE	12
CD8	SK1	FITC	0 0
CD16	873.1	PE	41
CD45	2D1	PerCp	10 0
CD19	SJ25C1	APC	0 3
CD23	CBVCS-5	PE	0 2
CD20	L27	APC	0 6
CD38	HB7	APC	16
CD10	Hl10a	FITC	0 0
CD56	NCAM16.2	APC	9 0
HLA-DR	L243	FITC	21
CD57	HNK-1	FITC	91
Kappa	TB28-2	FITC	01
Lambda	1-155-2	PE	01

Table 2: Panel used for immunophenotyping

Fluorochromes	FITC	PE	PerCP	APC
Tube1	lgG1	lgG1	CD45	lgG1
Tube2	CD2	CD7	CD45	CD56
Tube3	CD8	CD3	CD45	CD4
Tube4	CD10	CD20	CD45	Blank
Tubes	CD5	CD11c	CD45	CD19
Tube6	FMC7	CD23	CD45	CD20
Tube7	sKappa	slambda	CD45	CD19
Tube8	CD57	CD16	CD45	Blank

kappa/lambda light chain expression. In accordance with morphology [Figure 2] and immunophenotypic findings, a laboratory diagnosis of CD3+/CD4+/CD8-T-LGL was established. The patient was monitored, and no chemotherapy was administered. On follow-up at 6 months, the patient was asymptomatic with persistent cervical lymphadenopathy.

T-LGL was first described by McKenna *et al*.[6] in 1977. According to the WHO 2008 classification,[7] the diagnostic criterion for T-LGL is an LGL count exceeding 2 × 10^9/L for a period of more than 6 months. Immunophenotypically, CD4+ T-LGL is a clonal expansion of large granular lymphocytes that shows co-expression of NK cell-associated antigens – CD56 and CD57 – with variable expression of CD8 ($CD8^{-/+\ dim}$) and CD7 ($CD7^{-/+\ dim}$).[1] The index case fulfills the criteria for CD4+ T-LGL, both immunophenotypically and according to the WHO diagnostic criteria. Some studies have shown that CD4+/CD8-T-LGL proliferates

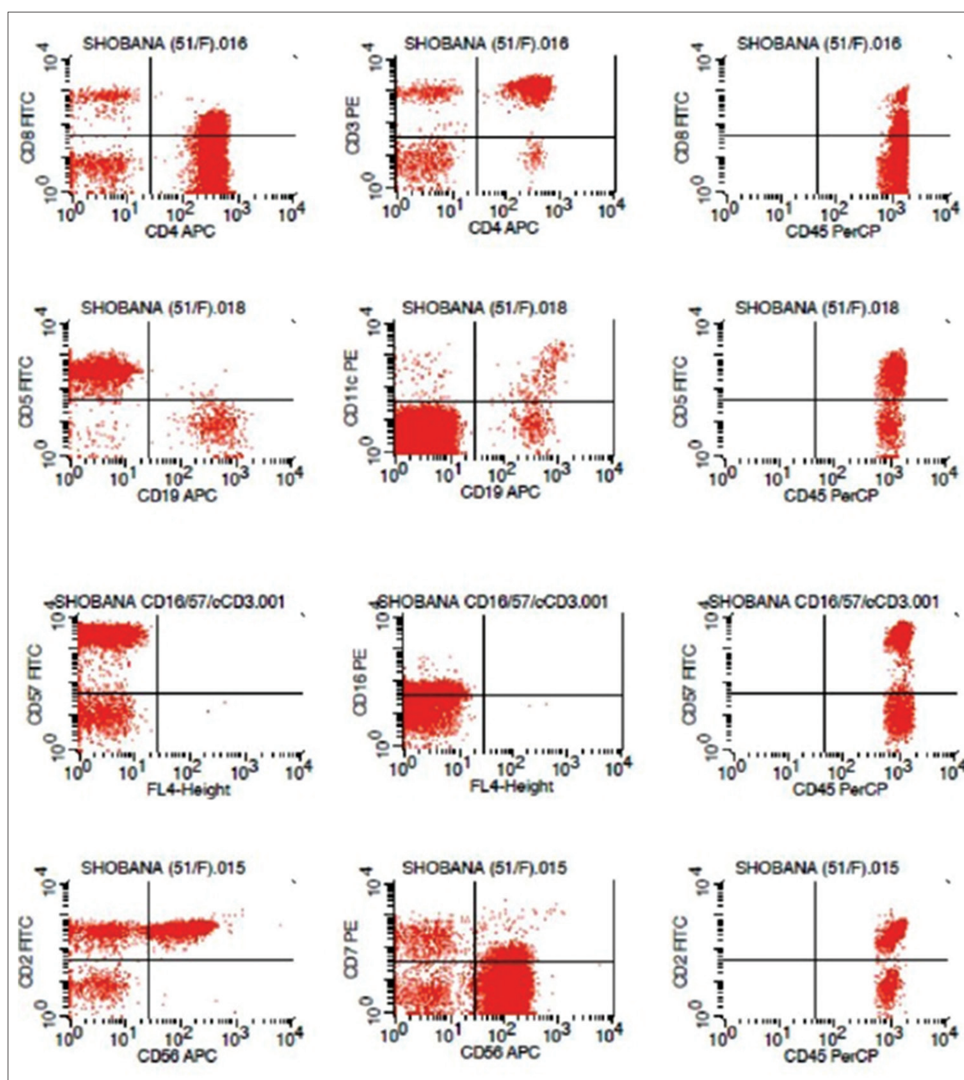

Figure 1: The cells showed positivity for CD3, CD4, CD5, CD2, CD16, CD56, and - CD57, indicating a T-cell origin. There was aberrant loss of CD7 expression, and CD8 expression was negative

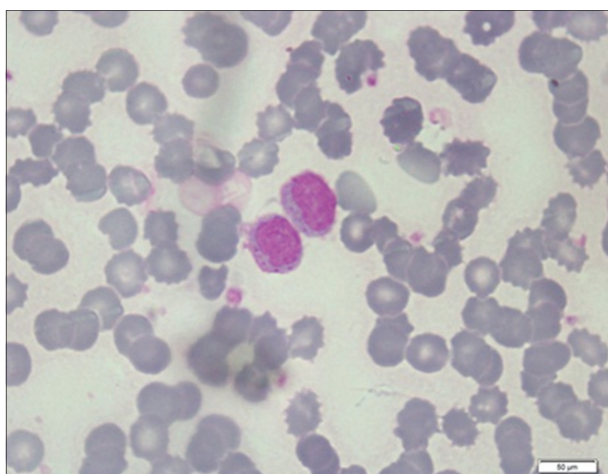

Figure 2: Giemsa stained peripheral blood film (×100) showing large granular lymphocytes

and expands as a result of tumor growth control by the immune system.[1] The leukemic clone blocks the normal Fas-mediated apoptosis of activated T-cells, thus leading to the etiopathogenesis of T-LGL.[8] Clinically, CD4+ T-LGL usually follows an indolent course with the absence of neutropenia, anemia, and splenomegaly. In contrast, CD8+ T-LGL presents with neutropenia, splenomegaly, and occasionally anemia. In view of indolent and nonprogressive nature of CD4+/CD8-T-LGL, these should be regarded as clonal expansions rather than leukemia.[3] Association of CD4+ T-LGL with other malignancies has been well described in the literature. Lima *et al*.[1] described a study of 33 patients with CD4+ and variable expression of CD8 ($CD8^{-/+\ dim}$) T-LGL, of whom 6 (18%) had a concomitant B-cell lymphoproliferative disorder (SMZL, lymphoplasmacytic lymphoma, typical B-chronic lymphocytic leukemia [B CLL], and atypical B CLL), and 3 (9%) had a nonhematological malignancy (thyroid carcinoma, gastric adenocarcinoma, and leiomyosarcoma). The patients presented with these malignancies either 2–4 years before,[1]1–4 years after,[1]

or at the same time they developed CD4+ T-LGL. Our patient, however, did not present with any secondary malignancies and has not developed any malignancies during the 6 months of follow-up after the diagnosis of CD4+ T-LGL. The subsequent monitoring will be continued at 3 monthly intervals till 4 years as described by Lima *et al*.,[1] who found secondary malignancies manifesting up to a time frame of 4 years after developing CD4+/CD8-T-LGL.

To conclude, CD4+/CD8-T-LGL is a T lymphoproliferative disorder that is distinct, both immunophenotypically and clinically, from CD8+/CD4-T-LGL. Patients should be closely monitored, as 18% and 9% of cases[1] are prone to develop secondary hematological and nonhematological malignancies, respectively. It will be too early to reach to ascertain this association in our case as she had a short clinical follow-up of 6 months and further needs a long follow-up (approximately 4 years).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Ashish Gupta, Anurag Bansal[1], Alok Kumar[1]

Departments of Hematology and Molecular Biology and [1]Hematology, Quest Diagnostics India Limited, Gurgaon, Haryana, India

Address for correspondence:
Dr. Ashish Gupta,
Flat No. 101, Tower 14, CHD Avenue, Sector 71, Gurgaon - 122 001, Haryana, India.
E-mail: ashishgupta.path@gmail.com

Submitted: 19-Jan-2018
Revised: 01-Mar-2018
Accepted: 27-Apr-2018
Published: 04-Dec-2019

References

1. Lima M, Almeida J, Dos Anjos Teixeira M, AlgueroMdMdel C, Santos AH, Balanzategui A, *et al*. TCR + /CD4 + large granular lymphocytosis: A new clonal T-cell lymphoproliferative disorder. Am J Pathol 2003;163:763-71.
2. Olteanu H, Karandikar NJ, Eshoa C, Kroft SH: Laboratory findings in CD4 (+) large granular lymphocytoses. Int J Lab Hematol 2010;32:e9-16.
3. Deepti M, Sharma RK, Kotru M, Saxena R. CD4+/CD8-/CD56+ T cell large granular lymphocyte proliferations; clonal disorders of uncertain significance. BMC Hematology 2014;14:9.
4. Rabade N, Mansukhani D, Khodaiji S, Padte B, Bhave A, Tembhare P, *et al*. Unusual immunophenotype of T-cell large granular lymphocytic leukemia: Report of two cases. Indian J PatholMicrobiol 2015;58:108-12.
5. Herling M, Khoury JD, Washington LT, Duvic M, Keating MJ, Jones D, *et al*. A systematic approach to diagnosis of mature T-cell leukemias reveals heterogeneity among WHO categories. Blood.2004;104:328-35.
6. McKenna RW, Parkin J, Kersey JH, Gajl-Peczalska KJ, Peterson L, Brunning RD. Chronic lymphoproliferative disorder with unusualclinical, morphologic, ultrastructural and membrane surface markercharacteristics. Am J Med 1977;62:588-96.
7. Swerdlow SH, Campo E, Harris NL, Pileri SA, Stein H, Thiele J, *et al*. WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues.Lyon: IARC; 2008.
8. Rose MG, Berliner N. T-cell large granular lymphocyte leukemia and related disorders. Oncologist 2004;9:247-58.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

How to cite this article: Gupta A, Bansal A, Kumar A. CD4+/ CD8- T cell large granular lymphocytic leukemia: A rare entity. Indian J Med Paediatr Oncol 2019;40:453-5.

© 2019 Indian Journal of Medical and Paediatric Oncology | Published by Wolters Kluwer - Medknow