Reviewer’s report

Title: CD4 positive/CD8 negative/CD56 positive T cell Large Granular Lymphocyte Proliferations. Clonal Disorders of Uncertain Significance.

Version: 2
Date: 27 February 2014
Reviewer: Horatiu Olteanu

Reviewer’s report:

The manuscript “CD4 positive/CD8 negative/CD56 positive T cell Large Granular Lymphocyte Proliferations; Clonal Disorders of Uncertain Significance.” by Mutreja et al. is a case report of two patients with persistent expansions of CD4(+)CD56(+) large granular T lymphocytes (LGLs). The authors report clinical, hematologic, immunophenotypic and laboratory findings in these patients that are in line with those reported by other groups.

This is an interesting topic, since CD4(+) large granular lymphocytoses are rare, and display different clinical and pathologic characteristics, compared to their more common CD8(+) counterpart, as shown by us and by other investigators. Of note, patients with CD4(+) large granular lymphocytoses appear to have a relatively benign clinical course, and some authors have put forth the hypothesis that these LGL proliferations represent reactive conditions, rather than true leukemias. While there is a known association with CMV infection, which further supports this hypothesis, in our opinion, the presence of multiple immunophenotypic aberrancies, in conjunction with demonstration of clonality, strongly support a neoplastic origin for these CD4(+) LGL expansions that do not occur in patients with a possible viral etiology.

The manuscript may benefit from considering following suggestions:

- Major Compulsory Revisions

1. Title: The authors should remove “clonal disorders of uncertain significance” from the title, as clonality has not been demonstrated in these T cell populations.
2. Abstract: The authors should remove “monotypic” from Case presentation: Case 1, unless they provide additional evidence to support this assertion.
3. Case presentation: Please provide reference ranges for hematologic parameters (CBC) and for CMV IgG titers.
4. Case presentation: The statement “T cell receptor (TCR) alphabeta restriction was seen and established monoclonality.” is incorrect, since the majority of normal circulating or bone marrow T lymphocytes are expected to express the alphabeta T cell receptor. Please perform additional testing (either Vbeta receptor analysis by flow cytometry or TCR RT-PCR) to substantiate the clonal nature of these T cell populations.
5. Case presentation: Please provide some information on the instrumentation
(flow cytometer, methodology) used to perform immunophenotyping, and whether CD7 expression was assessed. In our series of CD4(+) large granular lymphocytoses, CD7 was underexpressed in 7/8 cases, and constituted a useful and frequent immunophenotypic aberrancy.

6. Case presentation: The authors should comment on the presence of diffuse interstitial bone marrow infiltrates in Case 1, since it is uncommon for T-LGL leukemia to demonstrate this extensive amount and pattern of bone marrow involvement; intrasinusoidal distribution of LGLs would be a more common finding.

7. Case presentation: The authors should indicate whether the persistent lymphocytosis is composed of the same type of LGLs as initially described at diagnosis, at a minimum by confirming the morphology, if no repeat immunophenotypic information is available.

8. Discussion: The statement “Both patients in this series had CD4+/CD8-/CD56+ T-LGL with clonality ascertained by TCR alphabeta restriction.” is incorrect and should be removed (see comment #4)

- Minor Essential Revisions
1. Introduction: Please insert “leukemia” after “There are three notable variants of T-LGL”

- Discretionary Revisions
None.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests.