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**Contribution:** C.S. and G.S. designed and performed research, analyzed data, and wrote the paper; J.F.S., C.F., D.C., H.G., S.L., R.D., L.M.P., C.M., M.G.S., C.C.-C., and M.M. performed research and contributed data; and all authors edited and approved the manuscript.

**Conflict-of-interest disclosure:** C.S. and M.G.S. received honoraria from Roche. R.D. received honorarium and travel support from Roche. G.S. participated on Roche advisory boards, and received honoraria and research support from Roche. The remaining authors declare no competing financial interests.

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## To the editor:

### PLZF staining identifies peripheral T-cell lymphomas derived from innate-like T-cells with TRAV1-2-TRAJ33 TCR- $\alpha$ rearrangement

Peripheral T-cell lymphomas (PTCL) are uncommon and account for <10% of all non-Hodgkin lymphomas.<sup>1</sup> The most common category of PTCL is “not otherwise specified” (PTCL-NOS), reflecting the lack of specific parameters to define PTCL subsets in a biologically relevant way.<sup>2</sup> Although it is recognized that PTCL arise from both adaptive and innate lymphoid cells, the precise cell of origin for most PTCL cases remains unknown. Classically,  $\gamma\delta$  T-cell and true natural killer (NK) cell lymphomas are thought to arise from innate cells.<sup>3</sup> However, there are rare subsets of  $\alpha\beta$  T-cell populations, such as NK T-cells and mucosal-associated invariant T-cells (MAIT) that do not have described malignant counterparts. These cells have limited  $\alpha$  chain diversity and demonstrate an innate-like behavior by rapidly producing cytokines in response to antigen presentation by non-classical major histocompatibility complex class I molecules, even without previous priming.<sup>4</sup> These cells require the promyelocytic leukemia zinc finger (PLZF) transcription factor for development and maturation. Therefore, we determined if PLZF expression could identify PTCL derived from innate-like T-cells by performing immunohistochemistry with an anti-PLZF antibody on a tissue microarray generated using biopsies from 26 PTCL-NOS, 11 anaplastic large cell lymphomas (ALCL), anaplastic lymphoma kinase (ALK)<sup>-</sup>, and 13 ALCL, ALK<sup>+</sup>. Only rare positive cells were identified in normal tonsil, lymph node, and thymus (not shown). In contrast, the intestinal mucosa, which is normally enriched in PLZF<sup>+</sup> innate like T-cells, showed expression in 8% to 10% of lymphocytes (not shown). Using a cutoff of >20% of lymphoma cells with nuclear staining for PLZF, 2 of 26 PTCL-NOS cases were scored as positive (Figure 1A-D), but no ALCL, ALK<sup>+</sup> or ALCL, ALK<sup>-</sup> lymphomas met this criterion (Figure 1E-F). Because the innate-like T-cells are defined by the invariant T-cell receptor (TCR)- $\alpha$  rearrangements, we next performed polymerase

chain reaction followed by Sanger sequencing to determine the identity of the TCR- $\alpha$  V-J rearrangements. Both PLZF-positive cases showed the TRAV1-2-TRAJ33 TCR- $\alpha$  rearrangement (V $\alpha$ 1-2-J $\alpha$ 33) characteristic of MAITs.<sup>5</sup> No amplification was observed for the TRAV10-TRAJ18 rearrangement seen in NKT cells. Patient 1 presented with large bowel involvement and retroperitoneal lymphadenopathy and patient 2 with generalized lymphadenopathy. Bone marrow was involved in both patients. Both cases expressed CD2, CD3, CD4, and CD5. CD7 and partial CD30 expression was observed in case 1, whereas these antigens were not expressed in case 2.

In contrast to precursor T-lymphoblastic lymphoma/leukemia, PLZF expression is rare in PTCL with only one other positive case reported in the literature.<sup>6</sup> To our knowledge, this is the first report to demonstrate PTCL arising from MAITs, based on both PLZF staining and the V $\alpha$ 1-2-J $\alpha$ 33 gene rearrangement. Although rare, these cases likely represent a biologically unique group of PTCL that may be clinically relevant. It is well-known that innate T-cells are highly resistant to xenobiotics due to high expression of the transporter adenosine triphosphate-binding cassette B1 (ABCB1). Prospective evaluation for PLZF expression will be useful in identifying patients who will benefit from therapy targeting this pathway of drug resistance.

**Stephanie McGregor**

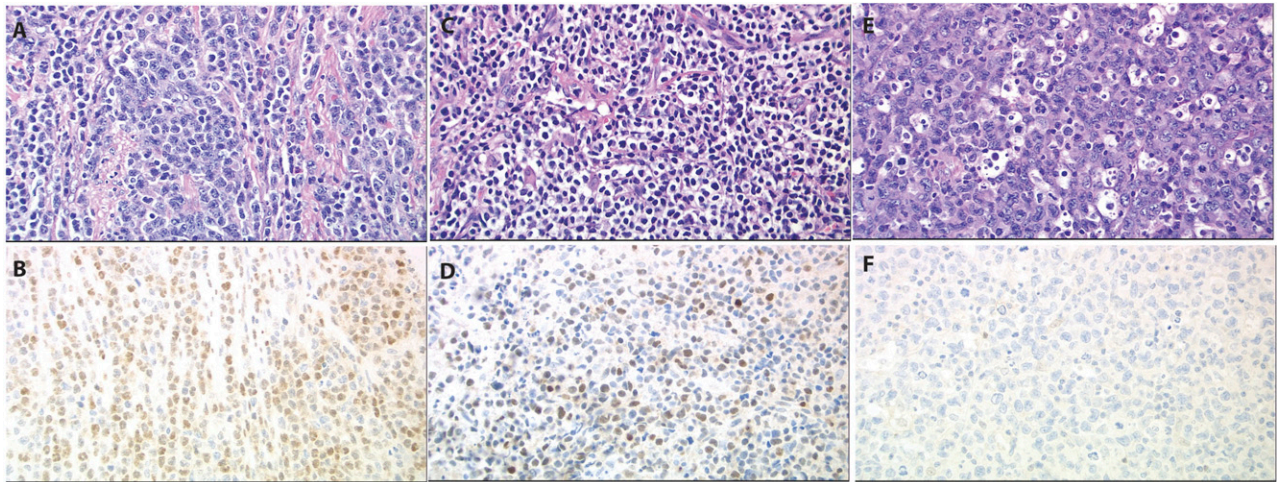
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Case 1 (A,B) Site	2 (C,D)	3 (E,F) Negative control
Large bowel	Lymph node	
Immunophenotype CD3+, CD5+, CD4+	CD3+, CD5+, CD4+	
Cytogenetics Complex	N/A	
Alpha chain V $\alpha$ 1-2 - J $\alpha$ 33	V $\alpha$ 1-2 - J $\alpha$ 33	

**Figure 1. PLZF expression identifies PTCL arising from innate-like mucosal-associated invariant T cells.** (A-F) Representative hematoxylin and eosin-stained sections of the two PLZF<sup>+</sup> cases (cases 1 and 2) and a PLZF- ALCL case (case 3) are shown in panels A, C, and E, respectively. The corresponding PLZF staining is shown in panels B, D, and F. Tumor site, immunophenotype, and the TCR- $\alpha$  rearrangements observed are shown below the respective positive cases. Complex karyotype seen in case 1 is as follows: 71~87,XXXX,t(1;3)(p36.3;q25),-3,-4,-5,-7,-8,-9,9,del(10)(p11.2p15) $\times$ 2,del(11)(q21q25) $\times$ 2,der(12)t(3;12)(q25;q24.3) $\times$ 2,dup(12)(q13q22)x2,-13,-14,-15,-16,-17,i(17)(q10),-18,+mar1x2,+mar2[cp11]. Photomicrographs are taken at magnification  $\times$ 500 for all panels.

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**Conflict-of-interest disclosure:** The authors declare no competing financial interests.

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**Acknowledgments:** This study was approved by the University of Chicago Biological Sciences Division Institutional Review Board (protocol 12-0190) and was carried out in compliance of the Declaration of Helsinki.

**Contribution:** S.M. and S.G. designed research, performed research, analyzed data, and wrote the manuscript; A.S. and E.H. performed research; G.R. and M.K.R. performed research and analyzed data; and J.A. and J.W.V. performed research, analyzed data, and edited the manuscript.