

# Hepatosplenic and Subcutaneous Panniculitis-Like $\gamma/\delta$ T Cell Lymphomas Are Derived from Different V $\delta$ Subsets of $\gamma/\delta$ T Lymphocytes

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Gamma/delta T cell lymphomas ( $\gamma/\delta$  TCL) represent rare, often aggressive types of T cell malignancy that are clinically and pathologically diverse. Most  $\gamma/\delta$  TCL occur as a hepatosplenic or subcutaneous type. To date, analysis of the T cell receptor  $\delta$  (TCR $\delta$ ) gene repertoire of hepatosplenic  $\gamma/\delta$  TCL ( $\gamma/\delta$  HSTCL) and subcutaneous panniculitis-like  $\gamma/\delta$  TCL ( $\gamma/\delta$  SPTCL) has been reported only in a limited number of cases. In this study we analyzed 11  $\gamma/\delta$  HSTCL and 4  $\gamma/\delta$  SPTCL by polymerase chain reaction and immunostaining to determine their usage of the V $\delta$  subtypes (V $\delta$ 1–6). It is noteworthy that 10 of 11  $\gamma/\delta$  HSTCL expressed the V $\delta$ 1 gene. The remaining case also expressed T cell receptor  $\delta$  (TCR $\delta$ ) as determined by flow cytometry and TCR $\delta$  rearrangement in Southern blot. However, the V $\delta$  gene expressed by this lymphoma could not be determined, which suggests usage of an as yet unidentified V $\delta$  gene. In striking contrast to the  $\gamma/\delta$  HSTCL, all 4  $\gamma/\delta$  SPTCL expressed the V $\delta$ 2 gene. Our data demonstrate that  $\gamma/\delta$  HSTCL are preferentially derived from the V $\delta$ 1 subset of  $\gamma/\delta$  T lymphocytes, whereas  $\gamma/\delta$  SPTCL are preferentially derived from the V $\delta$ 2 subset. The pattern of V $\delta$  gene expression in HSTCL and SPTCL corresponds to the respective, predominant  $\gamma/\delta$  T cell subsets normally found in the spleen and skin. This finding suggests that  $\gamma/\delta$  TCL are derived from normal  $\gamma/\delta$  T lymphocytes which reside in the affected tissues. Furthermore, the selective, lymphoma type-specific V $\delta$  gene segment usage may provide a molecular tool to distinguish better among various types of  $\gamma/\delta$  TCL lymphoma particularly in the clinically advanced, widely disseminated cases. (*J Mol Diag* 2000; 2:11–19)

Similar to normal T lymphocytes, T cell lymphomas (TCL) may express two different types of T cell receptor (TCR),  $\alpha/\beta$  or  $\gamma/\delta$ . Four TCR genes ( $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ ) are composed in their germline configuration of noncontiguous segments of variable (V), diversity (D), joining (J), and constant (C) regions. During T cell differentiation, somatic VDJ rearrangements occur and thereby generate variability of the TCR.<sup>1</sup> Only complete in-frame TCR gene rearrangements, consisting of V, D, and J regions, may form a functional TCR. Incomplete rearrangements between two D regions (D-D), between V and D region (V-D), and between D and J region (D-J) are nonfunctional. The majority of normal T lymphocytes express the  $\alpha/\beta$  heterodimer; however, approximately 5% of the T cells express the  $\gamma/\delta$  heterodimer.<sup>2</sup> In contrast to  $\alpha/\beta$  T lymphocytes, development of  $\gamma/\delta$  T cells is not dependent on expression of major histocompatibility complex (MHC) I or MHC II molecules.<sup>3–6</sup> Unlike  $\alpha/\beta$  T cells, which develop almost exclusively in thymus,  $\gamma/\delta$  T cells can be generated in extrathymic sites such as intestinal epithelium, skin, spleen, and fetal liver.<sup>7–9</sup> The exact function of  $\gamma/\delta$  T lymphocytes has not been fully elucidated, but some studies suggest a role for these cells in early immune responses to infections, autoimmune disorders, and cancer immune surveillance.<sup>9</sup>  $\gamma/\delta$  T cells share some features with CD8+  $\alpha/\beta$  T lymphocytes and with natural killer (NK) cells. They show MHC-dependent and MHC-independent cytotoxicity, produce lymphokines, and exhibit NK-like lytic activity.

$\gamma/\delta$  TCL represent a rare type of T cell malignancy. They comprise less than 10% of peripheral T cell lymphomas<sup>10</sup> and occur mostly at extranodal sites in hepatosplenic, subcutaneous, or intestinal form. Hepatosplenic

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