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624.HODGKIN LYMPHOMAS AND T/NK CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

T-Cell Lgll of the $\Gamma\delta$ Subtype: Clinically Relevant Fact or Academically Interesting Finding?

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Large granular lymphocyte leukemia (LGLL) is a rare group of mature T and NK cell lymphoproliferative disorders, with an annual incidence of 0.2 - 0.72 cases per 1 million individuals. Median age of onset is 65, with case prevalence roughly equivalent between sexes. T-Cell LGLL (T-LGLL) makes up 85-91% of cases. The majority of T-LGLL clones express T$\alpha\beta$, with only 5% of cases expressing T$\gamma\delta$. Outcomes and treatment data on this subtype is limited. Recent observational data suggest reduced overall survival (OS), increased incidence of cytopenias and associated autoimmune diseases, and favorable response to first line therapy with cyclosporine, in comparison to the T$\alpha\beta$ subtype. Here, we summarize disease biology and clinical presentation and provide review of recent literature describing clinical course and treatment options in the context of a patient case.

A woman in her early 70's with osteoporosis, asthma and hypertension presented to hematology after she was found to have leukocytosis of 12.1* 103/μL during routine lab work. CBC w/differential showed lymphocytosis of 11.0* 103/μL with absolute neutrophil count of 496 *103/μL and thrombocytopenia (121* 103/μL). She was asymptomatic without history of malignancy or autoimmune disease, prior available labwork was normal and physical exam was unremarkable. Peripheral smear showed atypical lymphocytes, with flow cytometry demonstrating 50.45% clonality with CD2+, CD3+, CD4-, CD7+, CD8 +/- , CD16+, CD 56-, CD57+/-, T$\gamma\delta$ + phenotype. Bone marrow biopsy demonstrated hypercellular (70%) marrow with scattered lymphoid aggregates with clonal infiltration of 20% core cellularity by CD3 immunohistochemistry. Bone marrow flow demonstrated the T-Cell phenotype seen in peripheral blood. T-Cell clonality study demonstrated TCR gamma chain rearrangement. PET/CT showed mildly increased FDG uptake throughout bone marrow. Next-Generation Sequencing confirmed mutations of STAT3 (D661Y), ASXL1, and TET2.

There is conflicting data on whether T$\gamma\delta$ positivity portends reduced OS compared to T$\alpha\beta$. Observational studies show that T$\gamma\delta$ is more frequently symptomatic and conveys higher risk of cytopenias. Not all cases require treatment. Treatment is usually prompted by single-lineage cytopenias. First line single agent therapy with methotrexate (MTX), cyclosporine, and cyclophosphamide have shown similar overall response rates of 40-50%, though STAT3 mutated disease is associated with better response to MTX. STAT3 mutations are associated with more severe cytopenias, more frequent autoimmune/inflammatory disorders, and more frequently required therapy, however neither STAT mutations nor cytopenias convey decreased OS in T$\gamma\delta$ disease. STAT3 and STAT5b mutations occur in 40% of all LGLL cases, with STAT3 mutations associated with neutropenia and rheumatoid arthritis. Nearly two thirds of *STAT3* genetic mutations are Y640F and D661Y.

Our patient was initiated on prednisone, though due to poor tolerance was transitioned to MTX titrated to 12.5 mg weekly. She has remained on this dose with good tolerability for 18 months with resolution of lymphocytosis and improvement in neutropenia.

T-LGLL has an OS of 9 years. Rarity of T$\gamma\delta$ disease has limited the ability to generate subtype specific survival data. The largest retrospective study to date included 137 T$\gamma\delta$ patients across 8 centers and provided a signal that T$\gamma\delta$ disease may predict reduced OS compared to the T$\alpha\beta$ subtype, however data was limited by disparate median follow-up time amongst cohorts due to high rates of censorship in the T$\gamma\delta$ cohort. Median OS was not reached at median follow up time of 48 months. This trend would be clinically expected given that T$\gamma\delta$ subtype has been consistently associated with severe cytopenias and autoimmune diseases, but should not be accepted until higher quality evidence is generated over longer median follow-up times. The same study found better responses to cyclosporine as first line therapy, an interesting observation as MTX has been generally accepted as first line therapy based on predominantly retrospective studies, though these studies did not stratify treatment responses by TCR phenotype. These findings underscore the need for prospective studies characterizing T$\gamma\delta$ specific disease course, survival analyses and treatment response.

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