Do *CXCR4* mutations impact disease presentation in WM?

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Background: Lymphoplasmacytic lymphoma (LPL) is a small B-cell lymphoma with recurrent mutations in *MYD88*in >90% of LPL cases. Recently, WHIM syndrome-like mutations in*CXCR4* have been identified in a fraction of LPL cases, and seem to impact clinical presentation and response to therapy. We thereforeinvestigated the presence of*MYD88* L265P and *CXCR4*mutationsin decalcified paraffin-embedded BM biopsies. Additionally, we investigated potential differences in clinical presentation between *CXCR4*^{WHIM} vs. *CXCR4*^{WT} cases.

Design: Decalcified FFPE BM biopsiesof 51 LPL cases were analyzed. For identification of *MYD88* L265P a LNA-clamped PCR with subsequent melting curve analysis was developed. A subset of cases was validated with Sanger sequencing. In addition, the C-terminal domain of *CXCR4* was sequenced in LPL cases.

Results: The median age of patients with LPL was 71 years (range 46 – 89) with a slight male predominance. The mean IgM level at diagnosis was 2952 mg/dl (range 95 – 7800). The extent of BM infiltration ranged from 5 – 100% (mean 42.5%). Only one case showed an IgGparaprotein.*MYD88* L265P was found in 49/51 (96%) LPL cases. Mutations in *CXCR4* were detected in 20/46 (43.5%) analyzed LPL cases. *CXCR4*^{WHIM} mutated LPL cases showed a significantly higher BM infiltration (p=0.023), and lower counts of hemoglobin (p=0.008), platelets (p=0.016) and leukocytes (p=0.029). In contrast, *CXCR4*^{WT} cases tended to have higher incidence of lymphadenopathy (41% vs. 22%). *CXCR4*^{nonsense} mutated cases showed significantly lower platelet countsand higher IgM levels at diagnosis, whereas *CXCR4*^{frameshift} mutated cases had a significantly lower hemoglobin level when compared to *CXCR4*^{WT} cases.

Conclusion: In this study we could show that *CXCR4*-mutated patients show ahigher extent of BM infiltration and lower levels of leucocytes, hemoglobin and platelets confirming the difference in clinical presentation between patients with mutated or WT *CXCR4*.In keeping with recent results, the *CXCR4* WT group shows a higher incidence of lymphadenopathy indicating a lower propensity for homing to the BM microenvironment compared to the*CXCR4*-mutated cases. Comparing *CXCR4*^{nonsense} with *CXCR4*^{framshift} mutations, we could not show a significant difference like in previous studies,nevertheless patients with *CXCR4*^{nonsense}mutations had higher IgM levels and lower platelet levels at diagnosis.