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Abstract Title: Associations of Chromosomal Aberrations with Clinical Aggressiveness and Shorter Time to Next Treatment in Symptomatic Waldenström's Macroglobulinemia
Special Instructions: Background: The clinicopathologic features and prognostic impact of MYD88 L265P mutation (MYDL265P), CXCR4 mutations (CXCR4Mut), chromosome 6q deletion (6q del), and chromosome 17p deletion (17p del) have been well reported. However, little is known about the impact of chromosomal aberrations (CAs) identified through conventional karyotypic analysis in symptomatic Waldenström's macroglobulinemia (sWM). Herein, we investigated the clinicopathologic features and cytogenetic/molecular abnormalities of sWM, with a particular focus on CAs.

Methods: We retrospectively analyzed clinicopathologic results, genetic mutations, 6q del, 17p del, and CAs. Digital droplet PCR, FISH analysis, and conventional karyotyping (G-banding) were performed on bone marrow samples taken from sWM cases diagnosed at our institute between April 2010 and March 2024. Karyotyping and FISH analysis were conducted according to the International System for Human Cytogenetic Nomenclature 2020 guidelines. We evaluated the relationships between clinicopathologic features, including time to next treatment (TTNT), and cytogenetic/mutational abnormalities.

Results: Thirty-five patients were enrolled in the study. Median age was 71 yrs. and median hemoglobin level was 10.1 g/dL. Median serum IgM and M-protein levels were 3,120 mg/dL and 3,000mg/dL, respectively. MYDL265P was found in 30/35 (85.7%), whereas CXCR4Mut was found in 3/35 (8.6%), including two frameshift mutations (CXCR4 S338, CXCR4 T318) and one nonsense mutation (CXCR4 S338). FISH analysis identified 6q del in 5/18 (28%), and 17p del in 2/31 (6.5%). CAs using G-banding were recognized in 9/34 (26%), including 4/34 (12%) with complex karyotypes.

The MYD88L265P/CXCR4Mut group had higher serum M-protein levels (p = .08), than the MYD88L265P/CXCR4WT group. Patients with 6q del had lower serum albumin level (5/5 [100%] vs. 7/13 [54%], p = .09). sWM with CAs had more anemia (p = .04), hypoalbuminemia (p = .007), higher serum M-protein (p = .03), and serum IgM levels (p = .03).
The median follow-up was 61 months. The median TTNT was 27 months for those with CAs, in contrast to 68 months for those without CAs (p = 0.14). No differences in TTNT or OS were observed as a consequence of the status of MYD88/CXCR4 and del 6q.

Conclusions: sWM with CAs exhibited greater clinical aggressiveness and shorter TTNT; however, the difference in TTNT was not significant, which may be due to the small sample size. The presence of CAs in sWM should be reconsidered alongside mutational status and FISH results for a more comprehensive understanding of the disease.
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Associations of Chromosomal Aberrations with Clinical Aggressiveness and Shorter Time to Next Treatment in Symptomatic Waldenström's Macroglobulinemia

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Background: The clinicopathologic features and prognostic impact of *MYD88 L265P* mutation (MYD^{L265P}), *CXCR4* mutations ($CXCR4^{Mut}$), chromosome 6q deletion (6q del), and chromosome 17p deletion (17p del) have been well reported. However, little is known about the impact of chromosomal aberrations (CAs) identified through conventional karyotypic analysis in symptomatic Waldenström's macroglobulinemia (sWM). Herein, we investigated the clinicopathologic features and cytogenetic/molecular abnormalities of sWM, with a particular focus on CAs.

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