In-depth molecular analysis using a multi-gene lymphoma NGS panel in lymphomas with lymphoplasmacytic differentiation may provide more precise diagnosis, differentiation of entities and may optimize rational treatment allocations

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Introduction:

Lymphoplasmacytic lymphoma (LPL) is a B-cell neoplasia defined by a variable mixture of lymphocytes, lymphocytes with plasmacytic differentiation and plasma cells and is known as Waldenstroems macroglobulinaemia (WM)(1,2). However, (lympho)plasmacytic differentiation can also be found in other low-grade B-cell lymphomas resulting in diagnostic complexities, only partly relieved by the detection of the MYD88 mutation (1,3-5). Clinically the presence or absence of either MYD88 and/or CXCR4 mutations has been shown to influence treatment response (6-8). Similarly, other oncogenic mutations indicate a poor outcome, though its impact on prognosis and treatment remains to be determined (6-8).

We attempted to integrate morphology and molecular pathology for a more precise diagnosis by performing next generation sequencing (NGS) in primary and relapsed LPL/WM.

Material and Methods

Next Generation sequencing

- 43 bone marrow trephine biopsies including primary diagnosis and relapses of 24 WM, 6 small B-cell lymphomas with plasmacytic differentiation (SBCL-PC) and 3 (IgM) MM patients.
- Lymphoma Panel (Lymphoma Solution, SophiaGenetics, Geneva, Switzerland) with 54 relevant genes.

Results

- MYD88 mutation in 95% and CXCR4 mutation in 25% of WM
- MYD88 mutation in 50% of SBCL-PC, but not in MM
- Novel BIRC 3 mutation described in a patient with progressive WM.

Type of Mutation	Missense mutation (%)	Nonsense mutation (%)	Frameshift mutation (%)	Splice-site mutation (%)
MYD88	37 (86.04%)	-	-	-
CXCR4	-	2 (4.6%)	10 (23.2%)	-
ARIDA1	1 (2.3%)	1 (2.3%)	6 (13.9%)	1 (2.3%)
KMT2D	5 (11.6%)	-	1 (2.3%)	-
TP53	4 (9.3%)	-	-	4 (9.3%)
POT1	2 (4.6%)	-	1 (2.3%)	-
TNFAIP3	3 (6.9%)	-	-	-

Table 1: Most frequently found mutations in the 43 trephine biopsies

- Oncogenic mutations are associated with progressive disease (p = 0.015) and transformation (p = 0.01); a low mast cell count is associated with progression (p = 0.022)
- a diffuse infiltration pattern predicts a worse PFS (see fig. 1).

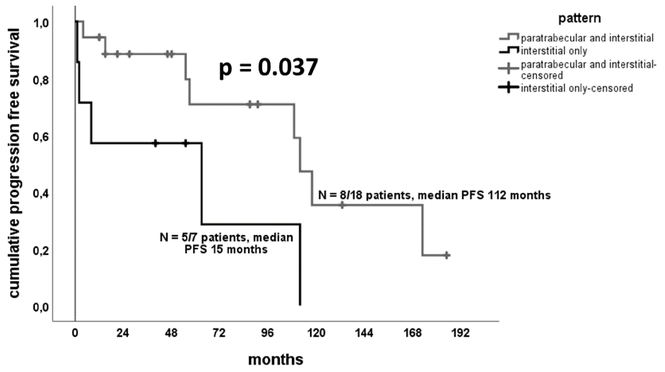

Figure 1: Kaplan-Maier survival analysis for progression free survival A significantly longer PFS was seen in patients with a paratrabecular and interstitial infiltration pattern compared to those with a purely interstitial pattern (N= number of events/number of patients)

Literature

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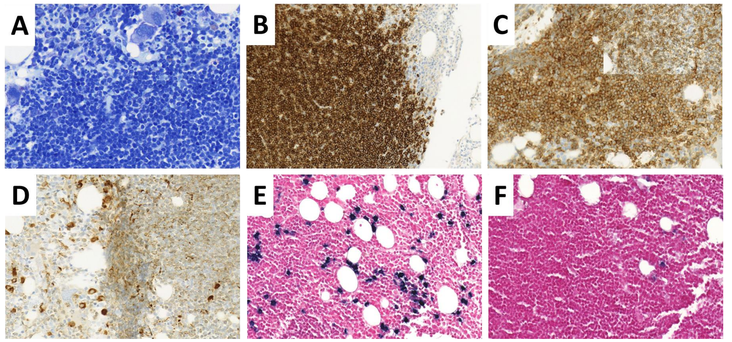

Figure 2: SBCL-PC finally diagnosed as CLL with a predominant lymphocytic infiltrate A) positive for CD20 (B), CD5 (C) and CD23 (C-inlet), but admixed clonal plasmacells (D – Vs38c; E and F: kappa and lambda in situ hybridisation) and MYD88L265P mutation

Discussion

- Assessment of classical morphological features is a prerequisite in the diagnosis of WM
- Careful morphological evaluation, immune phenotyping and molecular analysis in debatable cases best way to achieve a proper diagnosis
- Overlapping features exist in the SBCL-PC group including shared mutations with CLL such as POT1, FBXW7, XPO1.

Patients with LPL/WM might benefit from thorough pathological work-up and detailed molecular analysis in terms of a precise diagnosis and targeted treatment allocation.

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