W34: Discriminating between Waldenström's Macroglobulinemia and Marginal zone lymphoma using clinicopathological and molecular features.

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Objectives The differential diagnosis between Waldenström's Macroglobulinemia (WM) and marginal zone lymphoma (MZL) can be challenging. Bone marrow infiltration and serum monoclonal immunoglobulin IgM, the hallmarks of WM, can also be present in MZL. A somatic point mutation in myeloid differentiation primary response 88 gene (MYD88) L265P is present in 90-95% of WM patients. In addition, CXCR4 mutations have been reported in 20-30% of WM patients and are the second most common mutations found in WM. However, these mutations are also present in a minority (7-21% and 11%, respectively) of MZL patients. We sought to determine which characteristics are useful in the differential diagnosis between WM and MZL.

Methods In this study we reviewed the medical records of 93 WM patients and 47 MZL patients diagnosed according to the World Health Organization (WHO) guidelines. The clinical, histopathologic, immunophenotypic and molecular features at time of initial diagnosis of both diseases were extracted from the medical records and systematically reviewed. The study was complemented with MYD88 L265P mutation analysis of undetermined samples.

Results Serum monoclonal immunoglobulin was present in all patients with WM and only in 18 (38%) patients with MZL with a median concentration of 17,7 g/l (range 0,5-59,3) and 15,4 g/l (range 0,2-88,8) respectively (*P* = .09). As expected, serum IgM level was higher in WM patients with a median of 22,1 g/l (range 0,5-127) and 3,6 g/l (range 0,5-47,7) for MZL patients (*P* = <.0001). The most distinguishing clinical features of WM compared to MZL were the presence of anemia (*P* = 0,04), neuropathy (*P* = .001), and amyloidosis (*P* = 0,04). Lymphadenopathy (*P* = .002) was less frequently observed in WM. Histopathologically, all WM patients had bone marrow (BM) infiltration compared to 24 (52%) MZL patients (*P* <0,0001) and the median percentage of BM infiltration was 30% and significantly higher in WM compared to 15% in MZL (*P* = 0,01). The presence of lymphoplasmacytoid cells in the BM (*P* < .0001) and positive CD138 staining (*P* = .001) showed to be discriminating features. With flow cytometry, expression of CD49d and CD79b were identified as possible distinguishing markers. Finally, the presence of the MYD88 L265P mutation in 69 (86%) WM patients and 3 (8%) MZL patients showed to be of great value in the distinction between WM and MZL (*P* < 0,0001).

Conclusions Despite great overlap between these two disorders, a combination of clinical, histological, immunophenotypic and molecular characteristics can help distinguish WM from MZL. The presence or absence of high serum IgM, anemia, neuropathy, amyloidosis, high BM infiltration percentage with lymphoplasmacytoid cells, MYD88 mutation and potentially

flowcytometric markers should be weighed in complex, 'grey zone' cases. This study is currently being complemented with testing for the presence of CXCR4 mutations. A diagnostic algorithm will be developed and validated on two additional WM/MZL cohorts. Data will be updated at the time of the workshop.

Table I : Clinical, histopathological and molecular characteristics of patients with Waldenström macroglobulinema and Marginal zone lymphoma at the time of diagnosis

	n (%) or median (range)			
Characteristics	WM (*n* = 93)	MZL (*n* = 47)	odds ratio (CI)	*p* value
Age (years)	60 (29-85)	58 (21-83)	196,0	0,08
Gender			1,8 (0,9-3,7)	0,11
Male	55 (60%)	21 (45%)		
Female	37 (40%)	26 (55%)		
Anemia	57 (61%)	20 (43%)	2,1 (1,0-4,3)	0,04
Hb (range) (g/dL)	11,9 (5,6-15,6)	12,7 (6,6-16,2)	-	0,04
B-symptoms	33 (36%)	17 (36%)	1,0 (0,5-2,1)	1
Amyloidosis	7 (9%)	0 (0%)	0,9 (0,9-1,0)	0,04
Hyperviscosity syndrome	12 (13%)	1 (2%)	3,3 (0,4-26,8)	0,46
Neuropathy	21 (23%)	1 (2%)	13,4 (1,8-103,2)	0,001
Hemolytic anemia	6 (7%)	3 (6%)	1,1 (0,3-4,5)	1
Cryoglobulinemia	9 (10%)	2 (4%)	2,4 (0,5-11,8)	0,33
Lymphadenopathy	14 (15%)	18 (38%)	0,3 (0,1-0,6)	0,001
Splenomegaly	8 (9%)	10 (21%)	2,9 (1,1-7,9)	0,05
B2M (mg/l)	2,5 (1,4-12,6)	3,3 (1,5-4,9)	-	0,69
B2M>3 (mg/l)	61 (66%)	44 (94%)	7,7 (2,2-26,7)	<0,0001
Platelets (range) ($x10^9$/l)	261 (25-936)	221 (93-586)	-	0,02
WBC (range) ($x10^9$/l)	7,2 (1,3-94,3)	5,9 (2,3-33,2)	-	0,007
Presence of IgM M-protein	93 (100%)	18 (39%)	2,6 (1,8-3,7)	<0,0001
M-protein quantification g/l	15 (0,5-59,3)	6,2 (0,2-88,8)	-	0,09
Serum IgM g/l	22,1 (0,5-127)	3,6 (0,5-47,7)	-	<0,0001
BM involvement	92 (100%)	24 (52%)	1,9 (1,5-2,5)	<0,0001
Percentage of BM infiltration *(determined in 64 WM and 18 MZL)*	30% (5-100%)	15% (2-60%)	-	0,01
Lymphoplasmacytoid cells	64 (70%)	9 (21%)	8,9 (3,8-20,9)	<0,0001
CD138 staining *(determined in 66 WM and 20 MZL)*	54 (82%)	8 (40%)	6,8 (2,3-20,1)	0,001
MYD88 (L265P) mutation *(determined in 80 WM and 39 MZL)*	69 (86%)	3 (8%)	75,3 (19,7-287,1)	<0,0001
Flowcytometric expression of CD49d				0.028
Negative	(15%)	(10%)		
Postive	(40%)	(0%)		
Weak positive	(45%)	(90%)		
Flowcytometric expression of CD79b				0.005
Negative	(0%)	(40%)		
Positive	(81%)	(40%)		
Weak positive	(10%)	(20%)		

WM, waldenström macroglobulinemia; MZL, marginal zone lymphoma; BM, bone marrow; LDH, lactate dehydrogenase; B2M, β2 microglobulin; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; WBC, white blood cells