Abstract: P2064

Title: CHARACTERIZATION OF WALDENSTRÖM MACROGLOBULINEMIA WITH A FOCUS ON UNUSUAL IMMUNOPHENOTYPES: DIAGNOSTIC CLUES AND POTENTIAL BIOLOGICAL UNDERPINNINGS

Abstract Type: e-Poster Presentation

Topic: Indolent and mantle-cell non-Hodgkin lymphoma - Clinical

Background:

International experts' consensus acknowledges the key role of bone marrow (BM) biopsy for the diagnosis of Waldenström Macroglobulinemia (WM). Despite this, BM evaluation may pose diagnostic challenges, as (i) WM may be mimicked by other B-cell lymphomas (mainly,* marginal zone lymphoma [MZL]) and (ii) aberrant immunophenotypes occur in subsets of cases. Moreover, current evidence on the use of flow cytometry is based on data derived mostly from single centers' series. In this context, we sought to investigate whether a more refined immunophenotypic characterization of the neoplastic B cell clone performed trough immunohistochemistry may improve the diagnostic yield of WM, also contributing to shed light on its biological features.

Aims:

This study aimed at: (i) assessing the immunophenotype of WM with focus on unusual and/or underrecognized patterns; (ii) correlating phenotypic profiles with clinical-molecular data; (iii) assessing the role of immunophenotyping in the differential diagnosis with MZL.

Methods:

This retrospective study considered 76 cases of WM, diagnosed at Padua University Hospital (Padua – Italy) between 2017 and 2023. Data from the following points were considered: (i) clinical-laboratory presentation; (ii) treatments and outcome; (iii) BM morphology and phenotype by immunohistochemistry and flow cytometry; (iv) *MYD88* and *CXCR4* mutational status. A further series of 73 MZL cases was also considered to identify phenotypic features supporting the differential diagnosis with WM. Statistical analyses were performed by non-parametric tests for qualitative and quantitative variables.

Results:

The study population included 49 males and 27 females with median age at diagnosis of 71 (66-79) years. Median follow up time was 20 (9-38) months. BM biopsy disclosed a neoplastic lymphoid infiltrate ranging from 5% to 95% of total BM cellularity. Immunohistochemically, all cases were positive for pan-B cell markers, Bcl2 and MUM1, with variable expression of Bcl6 (18/72 [25%]; weak positivity in most cases), CD10 (3/67 [5%]), CD5 (7/33 [21%]) and MNDA (15/26 [58%]). CD23 was expressed in 57/76 (75%) cases, usually with partial/focal positivity (52/57 [91%]). Immunohistochemical results overlapped with flow cytometry data, with the notable exception of CD23, which was reported in only 18/46 (39%) cases by flow cytometry (likely result of the scarcity of positive events). CD23 expression was associated with lower prevalence of *MYD88*L265P mutations (14/18 [75%] in CD23-positive *vs* 48/50 [96%] in CD23-negative cases) and higher frequency of *CXCR4* mutations (3/8 [38%] *vs* 3/35 [9%], respectively) (p-value= 0.03 and 0.06, respectively). No clinical-pathological and/or molecular correlations were noted with other markers. Comparison with a similar subcohort of MZL cases highlighted a higher prevalence of CD23 expression in WM (57/76 [75%] *vs* 25/73 [34%], p-value <0.00001). No other markers were differently expressed between these entities.

Summary/Conclusion:

Immunohistochemical characterization highlights focal/partial CD23 expression as an underrecognized marker for the diagnosis of WM, which correlates with adverse disease molecular features (*MYD88*wt, *CXCR4*mut).

Immunohistochemical assessment for CD23 may add to the differential diagnosis with MZL.

	IHC CD23+ (n = 57)	**IHC CD23- (n = 19)**	**P value**
Age, years, median (IQR)	72 (66-80)	70 (64,5-72,5)	0,33
Lymphadenopathy or splenomegaly, n (%)	9/56 (0,16)	3/19 (0,16)	-
Therapy, n (%)	24/57 (0,42)	11/19 (0,58)	0,23
Hemoglobin, g/L, median (IQR)	130 (110-138)	120 (115-141,5)	0,88
Platelets, x 109/L, median (IQR)	243 (191-303)	227 (191-291)	0,54
B2-microglobulin, mg/L, median (IQR)	3,03 (2,27-4,39)	1,92 (1,88-2,76)	-
Monoclonal component IgM, g/L, median (IQR)	11,82 (7,15-21,49)	9,30 (7,00-14,60)	0,11
CRP, mg/L, median (IQR)	5,93 (2,90-15,00)	2,90 (2,90-4,93)	-
Bone marrow infiltration fraction, median (IQR)	30,00 (15,00-62,50)	20,00 (10,00-47,50)	0,34
MYD88^{L265P}, n (%)	48/50 (0,96)	14/18 (0,78)	**0,03**
CXCR4 mut, n (%)	3/35 (0,09)	3/8 (0,38)	**0,06**
Cytogenetic aberrations, n (%)	17/27 (0,63)	8/12 (0,67)	-
Complex karyotype, n (%)	5/17 (0,29)	1/8 (0,13)	0,62
IHC high expressed CD23, n (%)	5/57 (0,08)	0/19	-
Flowcytometry CD23 expression, n (%)	16/32 (0,50)	1/9 (0,11)	**0,05**
IHC coexpression CD5, n (%)	3/20 (0,15)	4/13 (0,31)	0.4
IHC coexpression MDNA, n (%)	13/21 (0,62)	2/3 (0,66)	-
IHC coexpression CD10, n (%)	3/51 (0,06)	0/16	-
IHC coexpression BCL6, n (%)	13/54 (0,24)	5/18 (0,27)	-
IHC coexpression MUM1, n (%)	45/47 (0,95)	15/16 (0,93)	-
IHC ratio kappa/lambda, median (IQR)	6,00 (1,00-10,00)	9,00 (4,50-10,00)	-

Keywords: Pathology, Waldenstrom’s macroglobulinemia, Immunophenotype, Lymphoid malignancy