Original Article

Access this article online



Website: www.ijhonline.org DOI: 10.4103/ijh.ijh 8 17

Immunohistochemical expression of SOX11 as a diagnostic tool for mantle cell lymphoma

Bassam M. Hameed

Abstract:

BACKGROUND: SOX11 is a transcription factor that has role in central nervous system development, it has found that this marker expressed in nuclei of mantle cell lymphoma and may play vital role in diagnosis and pathogenesis of mantle cell lymphoma.

AIMS: To evaluate the diagnostic role of SOX11 immunohistochemical expression in mantle cell lymphoma.

MATERIALS AND METHODS: A cross sectional study was designed, a total of 62 left over tissue samples (paraffin block of bone marrow biopsy) were included in the study. All the samples were taken from the Medical city/ teaching laboratories, and presented during the period 2014-2016. Cases diagnosed according to the WHO classification of mature B-cell Neoplasms with 26 cases having CLL/SLL, 17 were mantle cell lymphoma and 19 cases with follicular lymphoma. All the practical steps were carried out in teaching laboratories department of pathology and forensic medicine/ Al-Nahrain University - Collage Of Medicine. From each block, two sections were taken, and one were immunohistochemically stained for SOX11. And other section stained for haemtotoxylin and eosin stain.

RESULTS: In MCL, nuclear staining of SOX11 was seen in 16 (94.12%) of 17 patients, SOX11 nuclear staining was also seen in 1 case (3.85%) of 26 CLL/SLL cases, and 0 (0.0%) of 19 patients with FL. Furthermore, compared with CLL/SLL and FL, the positive rate of SOX11 nuclear staining was significantly higher in the MCL samples (P < 0.001). In addition SOX11 nuclear positivity had high sensitivity (94.12%) and specificity (97.78%) in diagnosis of MCL compared to Cyclin D1.

CONCLUSIONS: SOX11 is a powerful diagnostic tool for MCL, and may help in distinguishing it from other B-cell lymphoproliferative disoreders.

Keywords:

Immunohistochemistry, leiomyomatosis peritonealis disseminata, mantle cell lymphoma, SOX11

Introduction

Mantle cell lymphoma (MCL) is a subtype of non-Hodgkin's lymphoma (NHL), with aggressive clinical course, not so common reaching (5%–10%) of B-lymphoproliferative disorders (B-LPD), characterized by cyclin D1 expression and differentiated from possible morphologic imitators, comprising chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL) and follicular

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

lymphoma (FL) by CD5, CD23, and CD10 expression,^[1,2] as CD5 shared by both MCL and (CLL/SLL), but CD23 usually lacking in the former, while CD10 lands usually in FL. Nevertheless, CD23 negative CLL may also present.^[3]

Lately, SOX11, plays a major role in neurogenesis and remodeling, also has been found to be detected in the nuclei of MCL cells.^[4] Recent studies showed that both SOX11 mRNA and protein highly expressed in MCL irrespective to cyclin D1.^[5-7]

How to cite this article: Hameed BM. Immunohistochemical expression of SOX11 as a diagnostic tool for mantle cell lymphoma. Iraqi J Hematol 2017;6:17-20.

Department of Pathology and Forensic Medicine, College of Medicine, AL-Nahrain University, Baghdad, Iraq

Address for correspondence:

Dr. Bassam M. Hameed, Department of Pathology and Forensic Medicine, College of Medicine, AL-Nahrain University, Baghdad, Iraq. E-mail: bassamhematol@ gmail.com

Submission: 14-02-2017 Accepted: 11-03-2017 Furthermore, SOX11 showed to be expressed in more than 90% of MCL and in 100% of MCL with negative cyclin D1.^[8]

In this work, we studied SOX11 expression in a group of B-LPD through immunohistochemistry (IHC) to investigate whether nuclear staining of SOX11 can serve as a useful diagnostic marker for MCL.

Aims of the study

The aim of this study was to evaluate the diagnostic role of SOX11 immunohistochemical expression in MCL.

Materials and Methods

A cross-sectional study was designed; a total of 62 leftover tissue samples (paraffin block of bone marrow biopsy) were included in the study. All the samples were in use from the Medical city/teaching laboratories and presented during the period 2014-2016. Cases diagnosed according to the WHO classification of lymphoid neoplasms,^[9] with 26 cases having CLL/SLL, 17 were MCL, and 19 cases with FL. The diagnosis was made depending on flow cytometry reports and for MCL cases, diagnosis was confirmed by the demonstration of cyclin D1 expression by IHC. All the practical steps were carried out in teaching laboratories department of pathology and forensic medicine/Al-Nahrain University, College of Medicine. From each block, two sections of 5 µm thickness were taken; one section was immunohistochemically stained for SOX11 and the other for hematoxylin and eosin stain.

Immunohistochemical procedure for SOX11: the procedure was carried out according to manufacturer's instructions. Taking sections and mounted on Fisher brand positively charged slides. Then, slides deparaffinized and placed in DAKO antigen retrieval (pH 6). Later on, labeled streptavidin-biotin staining kit (Dako) used for staining, used for staining, after blocking endogenous peroxidase, and incubation of primary antibody (abcam mouse monoclonal anti-SOX11 antibody [CLO142] ab154138) at 20°C overnight.

Statistics

A nonparametric two-way contingency table Chi-square test or Fisher's exact test was employed, using Prism 7 for Mac OS X software, version 7.0a (Graph Pad Software, San Diego, California, USA). The validity of SOX11 in discrimination of MCL than other LPD was calculated using sensitivity, specificity, and positive and negative predictive values.

Results

Nuclear expression of SOX11 in MCL, CLL/SLL, and FL is demonstrated in [Table 1 and Figure 1]. In MCL,

nuclear staining of SOX11 was seen in 16 (94.12%) of 17 patients, and the staining was uniform and strong in mainstream of the neoplastic cells. In the remaining, one case of MCL had lacked staining of SOX11 in both nuclei and cytoplasm.

SOX11 nuclear staining was also seen in 1 (3.85%) of 26 CLL/SLL cases, with moderate nuclear expression and was negative in all (19) patients with FL [Figure 2].

Furthermore, compared with CLL/SLL and FL, the positive rate of SOX11 nuclear staining was significantly higher in the MCL samples (P < 0.001) [Table 1]. In addition, SOX11 nuclear positivity had high sensitivity (94.12%) and specificity (97.78%) in diagnosis of MCL compared to cyclin D1 [Table 2].

Discussion

LPDs include a wide variety of diseases, with variable prognosis and clinical behavior; for that, accurate measures for diagnosis are needed. MCL usually diagnosed depending on cyclin D1 expression; however, some negative cases do exist, this leads SOX11 to be potential nominee to differentiate MCL from other B-LPD.^[10,11]

Dictor *et al.* among other researchers studied the use of SOX11 in LPD, where their findings were not so specific for MCL diagnosis, while Zhang *et al.* work proved that nuclear staining of SOX11 was expressed in 54 (93.1%) of 58 MCLs, with other subtypes of LPD showed lower rate of positivity. This phenomenon might be explained due to different primary antibody kits used and numerous working practices used in IHC, the difference between these IHC results among different studies indicates that polyclonal antibody targeting SOX11 is not able to identify MCL from B-NHLs.^[5,11]



Figure 1: (a) Bone marrow trephine biopsy section, mantle cell lymphoma showing positive IHC nuclear staining for SOX11. Paraffin-embedded, ×10 objective.
 (b) Bone marrow trephine biopsy section, mantle cell lymphoma showing positive IHC nuclear staining for SOX11. Paraffin-embedded, ×40 objective

Hameed: Expression of SOX11 in mantle cell lymphoma



Figure 2: Bone marrow trephine biopsy section, chronic lymphocytic leukemia/small lymphocytic lymphoma showing negative IHC nuclear staining for SOX11. Paraffin - embedded, ×40 objective

Table 1: Nuclear SOX11 expression in mantle celllymphoma, chronic lymphocytic leukemia/small celllymphoma, and follicular lymphoma

	MCL	CLL	FL
SOX11 positive (%)	16 (94.12)	1 (3.85)	0
SOX11 negative (%)	1 (5.88)	25 (96.15)	19 (100.00)
Total	17	26	19
Р		<0.001**	

**P value significant <0.05. MCL = Mantle cell lymphoma, CLL = Chronic lymphocytic leukemia, FL = Follicular lymphoma

Table 2: Sensitivity and specificity of nuclear SOX11 staining compared to CCND1 expression

	MCL cyclinD1 positive	CLL/SLL and FL cyclinD1 negative
SOX11 positive	16	1
SOX11 negative	1	44
Total	17	45
Effect size	Value	95% CI
Sensitivity	94.12	73.02-99.7
Specificity	97.78	88.43-99.89
Positive predictive value	94.12	73.02-99.7
Negative predictive value	97.78	88.43-99.89
Likelihood ratio	42.35	

MCL = Mantle cell lymphoma, CLL = Chronic lymphocytic leukemia,

FL = Follicular lymphoma, CI = Confidence interval

Nordström *et al.* studied different NHL subtypes and nonmalignant bone marrow lymphoid disorders using monoclonal SOX11-C1 and lead to conclusion that monoclonal SOX11-C1 improves sensitivity and specificity of MCL detection as 100% of MCL cases showed bright nuclear staining while other tissues were negative for nuclear staining.^[12]

In this study, where monoclonal SOX11 antibodies were used, nuclear SOX11 expression was positive in

Iraqi Journal of Hematology - Volume 6, Issue 1, January-June 2017

16 (94.12%) out of 17 cases with MCL, which was in agreement with the majority of previous studies. $^{[1,5,7,13-15]}$

On the other hand, SOX11 nuclear expression was negative in most cases of CLL/SLL and all FL, which may confirm that monoclonal antibodies are far more sensitive (94.12%) and specific (97.78%) than polyclonal antibodies and more useful for MCL detection as earlier mentioned by other works.^[12,16]

There was one case of MCL that lacks nuclear SOX 11 expression in this work, this may be explained by variant of MCL which may show different clinical, phenotypic, and genetic characteristics. These cases presented with non-nodal MCL, leukemic phase and splenomegaly, with IGHV-mutated, and lacks SOX11 expression. On the other hand, classical types express SOX11 and may involve lymph nodes and other extranodal sites.^[17,18]

In addition to that, there was one case of CLL/SLL that expressed nuclear SOX11, this case may be cyclin D1 negative MCL presented as simulator to CLL/SLL, the differential diagnosis between MCL and CLL/SLL is crucial as MCL usually had aggressive clinical behavior. Both MCL and CLL share common phenotypic markers, usually CD19, CD20, and CD5. However, aberrant expression of these markers and the presence of cyclin D1 negative MCL may confuse the diagnostic process. For that, Wasik *et al.* suggest that using SOX11 in diagnostic flow cytometry would be of great value for accurate and trustworthy diagnosis of MCL.^[8,19]

Conclusion

Our study showed that SOX11 is a powerful diagnostic tool for MCL and may help in distinguishing it from other B-cell LPDs.

Financial support and sponsorship Nil.

Conflicts of interest

There are no conflicts of interest.

References

- 1. Ek S, Dictor M, Jerkeman M, Jirström K, Borrebaeck CA. Nuclear expression of the non B-cell lineage Sox11 transcription factor identifies mantle cell lymphoma. Blood 2008;111:800-5.
- Vose JM. Mantle cell lymphoma: 2015 update on diagnosis, risk-stratification, and clinical management. Am J Hematol 2015;90:739-45.
- 3. Abdel-Ghafar AA, El Din El Telbany MA, Mahmoud HM, El-Sakhawy YN. Immunophenotyping of chronic B-cell neoplasms: Flow cytometry versus immunohistochemistry. Hematol Rep 2012;4:e3.
- 4. Wang X, Asplund AC, Porwit A, Flygare J, Smith CI,

Hameed: Expression of SOX11 in mantle cell lymphoma

Christensson B, *et al.* The subcellular Sox11 distribution pattern identifies subsets of mantle cell lymphoma: Correlation to overall survival. Br J Haematol 2008;143:248-52.

- Dictor M, Ek S, Sundberg M, Warenholt J, György C, Sernbo S, *et al.* Strong lymphoid nuclear expression of SOX11 transcription factor defines lymphoblastic neoplasms, mantle cell lymphoma and Burkitt's lymphoma. Haematologica 2009;94:1563-8.
- 6. Lu TX, Li JY, Xu W. The role of SOX11 in mantle cell lymphoma. Leuk Res 2013;37:1412-9.
- Mozos A, Royo C, Hartmann E, De Jong D, Baró C, Valera A, et al. SOX11 expression is highly specific for mantle cell lymphoma and identifies the cyclin D1-negative subtype. Haematologica 2009;94:1555-62.
- 8. Narurkar R, Alkayem M, Liu D. SOX11 is a biomarker for cyclin D1-negative mantle cell lymphoma. Biomark Res 2016;4:6.
- 9. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC; 2008.
- Fu K, Weisenburger DD, Greiner TC, Dave S, Wright G, Rosenwald A, *et al.* Cyclin D1-negative mantle cell lymphoma: A clinicopathologic study based on gene expression profiling. Blood 2005;106:4315-21.
- Zhang LN, Cao X, Lu TX, Fan L, Wang L, Xu J, *et al.* Polyclonal antibody targeting SOX11 cannot differentiate mantle cell lymphoma from B-cell non-Hodgkin lymphomas. Am J Clin Pathol 2013;140:795-800.
- Nordström L, Andréasson U, Jerkeman M, Dictor M, Borrebaeck C, Ek S. Expanded clinical and experimental use of SOX11 - Using a

monoclonal antibody. BMC Cancer 2012;12:269.

- 13. Chen YH, Gao J, Fan G, Peterson LC. Nuclear expression of Sox11 is highly associated with mantle cell lymphoma but is independent of t(11;14)(q13;q32) in non-mantle cell B-cell neoplasms. Mod Pathol 2010;23:105-12.
- Hsiao SC, Cortada IR, Colomo L, Ye H, Liu H, Kuo SY, et al. SOX11 is useful in differentiating cyclin D1-positive diffuse large B-cell lymphoma from mantle cell lymphoma. Histopathology 2012;61:685-93.
- Zeng W, Fu K, Quintanilla-Fend L, Lim M, Ondrejka S, Hsi ED. Cyclin D1-negative blastoid mantle cell lymphoma identified by SOX11 expression. Am J Surg Pathol 2012;36:214-9.
- Righi S, Pileri S, Agostinelli C, Bacci F, Spagnolo S, Sabattini E. Reproducibility of SOX-11 detection in decalcified bone marrow tissue in mantle cell lymphoma patients. Hum Pathol 2017;59:94-101.
- Palomero J, Vegliante MC, Eguileor A, Rodríguez ML, Balsas P, Martínez D, *et al.* SOX11 defines two different subtypes of mantle cell lymphoma through transcriptional regulation of BCL6. Leukemia 2016;30:1596-9.
- Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, *et al.* The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375-90.
- Wasik AM, Priebe V, Lord M, Jeppsson-Ahlberg Å, Christensson B, Sander B. Flow cytometric analysis of SOX11: A new diagnostic method for distinguishing B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma from mantle cell lymphoma. Leuk Lymphoma 2015;56:1425-31.

