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 disorders.

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 lymphoma (FL) by CD5, CD23, and CD10 expression, 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.

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

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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]
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16 (94.12%) out of 17 cases with MCL, which was in agreement with the majority of previous studies.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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 \textit{et al.} suggest that using SOX11 in diagnostic flow cytometry would be of great value for accurate and trustworthy diagnosis of MCL.\textsuperscript{[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.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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