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Original Contribution

TP53 mutations are common in mantle cell lymphoma, including the indolent leukemic non-nodal variant

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ABSTRACT

Introduction: Mantle cell lymphoma (MCL) is an aggressive B-cell neoplasm, but clinically indolent subtypes are also recognized. Data on the utility of mutation profiling in the context of routine workup and its role in risk-stratification of MCL patients are limited. In this study, we describe the mutational landscape and clinicopathologic correlates of a series of MCL cases at a single-institution setting.

Methods: Samples from 26 patients with MCL were evaluated by NGS using DNA extracted from peripheral blood (PB) or bone marrow (BM). Evaluation of extent of PB or BM involvement was performed using flow cytometry immunophenotyping.

Results: The study group included 17 (65%) men and 9 (35%) women with a median age of 65 years (range, 50–94). Twenty-one (81%) patients had nodal MCL (N-MCL) and 5 (19%) had the "leukemic variant" (L-MCL). Mutated genesincluded *TP53* (35%), *ATM* (27%), *CARD11* (10%); and *FBXW7*, *NOTCH1*, *SPEN*, *BIRC3* (~5% each). Most mutations were clonal in nature. Ten unique *TP53* mutations were identified in 9 samples, including 3 L-MCL cases. There was no difference in the frequency of *TP53* mutations between L-MCL and N-MCL groups ($p = 0.3$), but *TP53* mutations were subclonal in 2/3 L-MCL cases. Identification of clonal *TP53* alterations in L-MCL patients prompted initiation of therapy despite low tumor burden.

Conclusions: *TP53* is commonly mutated in MCL. *TP53* mutations may be clonal or subclonal. Seemingly indolent L-MCL may harbor subclonal *TP53* mutations which may serve as a useful biomarker for prognostication, therapeutic planning, follow-up monitoring, and early detection of clonal expansion.

1. Introduction

Mantle cell lymphoma (MCL) has been long considered an aggressive mature B-cell lymphoma, derived from CD5 positive naïve B cells, with most patients ultimately relapsing and succumbing to disease despite intensive therapy [1,2]. MCL is caused by juxtaposition of *CCND1* located at chromosome 11q13 with the promoter region of *IGH* at chromosome 14q32 resulting in overexpression of cyclin D1. The *CCND1-IGH* translocation is a disease defining genetic abnormality and is believed to be the primary oncogenic event in MCL [3], although rare cases of chronic lymphocytic leukemia with acquisition of *CCND1-IGH* have been described [4]. This translocation is detected in > 90% of MCL cases and is usually detected by conventional karyotyping or fluorescence in situ hybridization [5,6]. However, studies using conventional cytogenetics, comparative genomic hybridization and other methods have shown the presence of many other chromosomal alterations in MCL [7-9]. In this regard, MCL is considered to be a genetically heterogeneous mature B cell neoplasm with many secondary chromosomal changes, likely resulting primarily from marked chromosomal instability [3,10,11].

More recently, a subset of MCL cases has been identified that shows mostly an indolent clinical course even without therapeutic intervention [7,12,13]. The 2016 update of the World Health Organization (WHO) classification of lymphoid neoplasms recognizes two indolent variants of mantle cell lymphoma: in situ mantle cell neoplasia and so-called non-nodal leukemic variant of mantle cell lymphoma (L-MCL) [5]. L-MCL shows a number of differences compared with nodal mantle cell lymphoma including frequently hypermutated immunoglobulin heavy chain variable region (*IGHV*), a less complex genome, and absence of SOX11 expression [12,14,15]. L-MCL frequently expresses surface CD200, which is usually absent in conventional nodal mantle cell lymphoma (N-MCL) [16]. The presence of secondary molecular

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changes, including alterations in *CDK4*, *INK4a*, *TP53*, *RB1* and *ATM*, are significantly more common in the N-MCL compared with L-MCL [17,18]. While MCL is generally considered to be incurable and is associated with poor prognosis in most patients, precise prediction of clinical outcome and prognosis of MCL patients is challenging due to disease heterogeneity [19,20].

TP53 mutations occur in approximately 5–11% of MCL cases and are associated with an unfavorable clinical outcome and poor response to conventional chemotherapy regimens [21]. Earlier studies have shown that MCL has a unique mutational profile with prognostic implications [22,23]; however, data on the utility of mutation profiling using next-generation sequencing (NGS) in the context of routine clinical workup and its role in risk-stratification of MCL patients, are limited. In this study, we describe the mutational landscape and clinicopathologic correlates of a series of MCL cases at a single-institution setting.

2. Materials and methods

2.1. Study group

This study was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center and was carried out in accord with the Declaration of Helsinki. We performed an electronic query of our departmental archives for patients diagnosed with MCL –with available next generation sequencing data. A total of 26 cases were identified. Clinical, laboratory and imaging data were obtained from electronic medical records.

2.2. Histologic evaluation

The diagnosis of MCL was established and cases were further subcategorized into N-MCL and L-MCL variants, based on criteria specified in the WHO classification [5]. Briefly, patients with peripheral blood (PB), bone marrow (BM) and/or splenic involvement without overt lymphadenopathy (< 1.5 cm) were considered L-MCL and cases with significant nodal involvement with or without extra-nodal involvement were considered conventional N-MCL [15]. All patients had BM involvement regardless of disease variant.

2.3. Flow cytometry and immunohistochemistry

Evaluation of the extent of PB or BM involvement was performed using flow cytometry immunophenotyping and immunohistochemistry as described previously [16]. Immunohistochemical studies were performed in a subset of cases on formalin-fixed, paraffin-embedded (FFPE) tissue sections with an automated immunostainer (BOND III; Leica Biosystems, Buffalo Grove, IL, USA). The antibodies used and their dilutions were as follows: CD20 (dilution 1:400), cyclin D1 (1:350), (Dako, Carpinteria, CA, USA); CD5 (1;20) (ThermoScientific, Fremont, CA, USA); SOX11 (1:200) (Cell Marque, St. Louis, MO, USA); and PAX5 (1:35) (BD Biosciences) (Supplementary Fig. 1). Flow cytometry immunophenotypic analysis was performed using standard multicolor analysis (FACS Canto II instrument, Becton Dickinson, San Jose, CA, USA). The lymphocyte population was gated according to right-angle side scatter and CD45 expression. The panel of monoclonal antibodies included varying combinations of reagents specific for CD3, CD5, CD10, CD11c, CD19, CD20, CD22, CD23, CD38, CD43, CD79b, CD200, FMC-7, and surface immunoglobulin light chains (Becton-Dickinson, Biosciences, San Jose, CA) (Supplementary Fig. 2).

2.4. Cytogenetic studies

Conventional cytogenetic analysis was performed on unstimulated cultured BM aspirate specimens using standard GTG-banding as described previously [24]. At least 20 metaphases were analyzed. Results were reported using the 2016 International System for Human Cytogenetic Nomenclature (ISCN).

Fluorescence in situ hybridization (FISH) for *MYC* rearrangement was performed in a large subset of cases (n = 23) on interphase nuclei obtained from cultured PB or BM cells using a LSI *MYC* dual color breakapart rearrangement probe (Abbott Molecular Downers, IL, USA.). This probe hybridizes to band 8q24.2, spectrum orange on the centromeric side and spectrum green on the telomeric side of the *MYC* breakpoint. A total of 200 interphases were analyzed. The 95% ($p < 0.05$) confidence limit of LSI *MYC* probe established in our laboratory is 0.6%–3.4%.

FISH for *CCND1/IGH* was performed on cultured PB or BM cells in a large subset of cases (n = 23) using the LSI *IGH/CCND1* dual color dual fusion translocation probe (Abbott Molecular, Downers, IL, USA). At least 200 interphase nuclei were analyzed. The 95% ($p < 0.05$) confidence limit of LSI *IGH/CCND1* probe established in our laboratory is 2%.

2.5. Next-generation sequencing

Next-generation sequencing-based mutation analysis (Illumina, San Diego CA, USA) was performed using DNA extracted from PB or BM aspirate samples using one of two panels. In 21 cases (L-MCL, n = 4; N-MCL, n = 17), a 29-gene whole-exome amplicon-based panel was used that included: *ATM*, *BIRC3*, *BTK*, *CALR*, *CARD11*, *CD79A*, *CD79B*, *CHD2*, *CSMD3*, *CXCR4*, *DDX3X*, *EZH2*, *FAT1*, *FBXW7*, *KLHL6*, *LRP1B*, *MAPK1*, *MUC2*, *MYD88*, *NOTCH1*, *PLCG2*, *PLEKHG5*, *POT1*, *SF3B1*, *SPEN*, *TGM7*, *TP53*, *XPO1*, and *ZMYM3*; and in 5 cases (L-MCL, n = 1; N-MCL, n = 4) a 53-gene hotspot amplicon-based panel was used that included: *ABL1*, *AKT1*, *ALK*, *APC*, *ATM*, *BRAF*, *CDH1*, *CDKN2A*, *CSF1R*, *CTNNB1*, *DNMT3A*, *EGFR*, *ERBB2*, *ERBB4*, *EZH2*, *FBXW7*, *FGFR1*, *FGFR2*, *FGFR3*, *GNA11*, *GNAQ*, *GNAS*, *HNF1A*, *HRAS*, *IDH1*, *IDH2*, *JAK2*, *JAK3*, *KDR*, *KIT*, *KLHL6*, *KRAS*, *MET*, *MLH1*, *MPL*, *NOTCH1*, *NPM1*, *NRAS*, *PDGFRA*, *PIK3CA*, *PTEN*, *PTPN11*, *RB1*, *RET*, *SMAD4*, *SMARCB1*, *SMO*, *SRC*, *STK11*, *TP53*, *VHL* and *XPO1*.

2.6. Clonal vs. Subclonal gene mutation

Clonality or subclonality of a gene mutation was determined by taking into account the percentage of leukemic cells as assessed by flow cytometry and comparing that to the variant allelic frequency (VAF) of the mutation of interest. Mutations with a heterozygous VAF ± 10% were considered clonal and those with a lower VAF were considered subclonal.

2.7. Statistical analysis

Statistical analysis was performed using GraphPad Prism 7 and IBM SPSS Statistics 22.0. Fisher's exact test and Mann-Whitney *U* test were used to assess categorical and continuous variables, respectively. The Spearman rank method was used to assess correlations. A *p*-value under 0.05 was considered significant.

3. Results

3.1. Clinical and laboratory findings

A total of 26 MCL patients were included in this study: 21 (81%) had N-MCL and 5 (19%) had L-MCL. All the patients had BM and/or PB involvement. There were 17 men (65%, 15 N-MCL and 2 L-MCL) and 9 women (35%, 6 N-MCL and 3 L-MCL). The median age for the entire patient cohort was 65 years (range, 50–94) at initial diagnosis. The median age at the time of diagnosis was 64 years (range, 50–94) and 71 years (range, 53–86) for N-MCL and L-MCL, respectively. For the entire cohort, the median absolute neutrophil count (ANC), hemoglobin (Hgb) and platelet (plt) count were 4.2 k/μL (range, 2.1–25.4), 12.5 g/

Table 1
Clinical and laboratory characteristics of study group. Only absolute lymphocyte count (ALC) at the time of diagnosis was significantly different between nodal and leukemic mantle cell lymphoma (ALC, absolute lymphocyte count; ANC, absolute neutrophil count; FCI, flow cytometry immunophenotyping; Hb, hemoglobin; MCL, mantle cell lymphoma; Plt, platelet).

	MCL n = 26	N-MCL n = 21 (81%)	L-MCL n = 5 (19%)	*p* value
Men:women	17:9	15:6	2:3	0.3
Age – median (range)	65 y (50–94)	65 (50–94)	70 (53–86)	0.7
% MCL by FCI	21 (3–80)	15 (3–80)	29 (16–61)	0.2
ANC (k/μL) –median (range)	4.2 (2.1–25.4)	3.9 (2.1–25.4)	4.2 (2.7–5.7)	0.7
ALC (k/μL) – median (range)	4.1 (0.4–144)	2.5 (0.4–144)	10.3 (7.5–17.6)	0.02*
Hb (g/dL) – median (range)	12.5 (8.6–15.9)	11.8 (8.6–15.9)	13.5 (10.8–14.2)	0.4
Plt (k//μL) – median (range)	166 (34–284)	157 (34–234)	242 (70–284)	0.1

* Statistically significant difference.

dL (range, 8.6–15.9), and 166 k/μL (range, 34–284), respectively. The median absolute lymphocyte count (ALC) for the entire cohort was 4.1 k/μL (range, 0.4–144); 2.5 (range, 0.4–144) for N-MCL and 10.3 (range, 7.5.8–17.6) for L-MCL ($p = 0.02$). The clinical and laboratory characteristics are summarized in Table 1.

3.2. Pathologic features

Twenty-five cases showed classical morphology and 1 case (# 7) showed blastoid morphology. All patients with N-MCL had lymph node involvement. Many patients also showed additional extramedullary sites of involvement detected by staging imaging studies. All cases were positive for cyclin-D1 by immunohistochemistry (n = 26). SOX11 expression was assessed in 14 cases (11 N-MCL and 3 L-MCL) and was positive in 10/11 (91%) N-MCL cases and 0/3 L-MCL cases ($p = 0.01$).

3.3. Immunophenotype

Flow cytometric evaluation of BM samples showed a median of 15% (range, 3–80%) lymphoma cells in N-MCL and 29% (range, 16–61%) in L-MCL($p = 0.39$). All cases showed immunoglobulin light chain restriction; 14 kappa and 12 lambda. Among L-MCL cases, 4/5 (80%) were kappa restricted whereas 10/21 (48%) of N-MCL were kappa restricted ($p = 0.33$). The MCL cells were positive for CD5 in 22 of 23 cases; the negative case (# 22) was L-MCL. CD38 was expressed in 19/21 (90%) N-MCL and 2/5 (40%) L-MCL ($p = 0.033$). CD200 was positive in 2 2/21 (9.5%) of N-MCL and 1/5 (20%) L-MCL cases ($p = 0.49$).

3.4. Cytogenetic findings

Conventional cytogenetic analysis was performed on BM aspirates or PB of 19 cases and t(11;14)(q13;q32) was detected in 14 cases. Five (26%) cases showed t(11;14) as a part of a complex karyotype, including 1 case of L-MCL. FISH analysis showed *CCND1-IGH* in all 23 cases assessed including 18 N-MCL and 5 L-MCL. (Table 3) FISH analysis for 17p deletion was not performed on any of the cases, however the conventional karyotype showed deletion 17 in two cases (cases #13 and 23). All 5 cases negative for t(11;14) by conventional cytogenetics were positive by FISH. The median percentage of BM cells harboring the *CCND1-IGH* translocation by FISH was significantly higher in L-MCL cases compared with N-MCL cases (60% vs. 20%, $p = 0.028$). (Table 3).

3.5. Gene mutations

Sixteen of 26 (62%) cases had at least one gene mutation. (Fig. 1 and Table 3) This included all 5 (100%) L-MCL and 11 of 19 (52%) N-MCL. The most commonly mutated gene was *TP53* (n = 9; 34.6%). *TP53* mutated cases included 3 of 5 (60%) L-MCL and 6 of 21 (28.5%) N-MCL ($p = 0.3$). (Tables 2 and 3) We used the percentage of leukemic cells as assessed by flow cytometry to infer the overall percentage of sample involvement and used this estimate as a means to determine the clonal versus subclonal nature of *TP53* mutations. All N-MCL cases (6/6, 100%) harbored clonal *TP53* mutations whereas 2 of 3 (67%) L-MCL cases had subclonal *TP53* mutations ($p = 0.08$). (Fig. 2) *ATM* was mutated in 7 (26.9%) of all cases (6 N-MCL and 1 L-MCL). *NOTCH1* (n = 1, 20%) and *BIRC3* (n = 1, 20%) mutations were limited to the L-MCL cases whereas *CARD11* (n = 2, 10%), *FBXW7* (n = 1, 5%), and *SPEN* (n = 1, 5%) mutations were limited to the N-MCL cases.

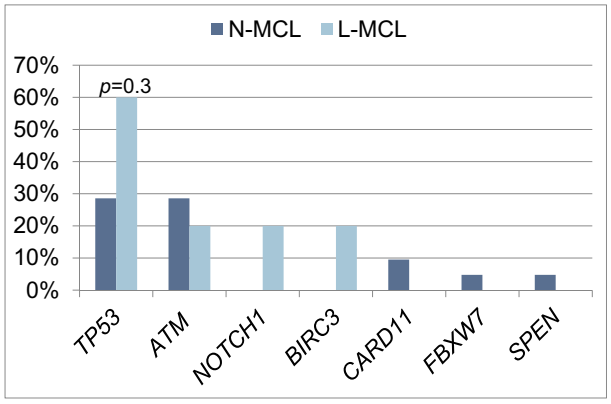

Fig. 1. Summary of gene mutations. Both *TP53* and *ATM* mutations were seen in N-MCL and L-MCL while the other genes were mutually exclusive between two types. *TP53* mutation was more common in the L-MCL.

Table 2
Mantle cell lymphoma cases with *TP53* mutation at the time of diagnosis. Percentage of lymphoma cells in flow cytometry (FC) analysis of diagnostic specimen is shown in first column. Variant allele frequency (VAF) and the actual *TP53* gene mutation are shown in second column.

	% MCL by FC	Mutation details [variant allele frequency]
L-MCL	47	NM_000546.5(*TP53*):c.734G > A p.G245D [1.0]
	16	NM_000546.5(*TP53*):c.743G > A p.R248Q [6.1]
	27	NM_000546.5(*TP53*):c.623A > T p.D208V [17.9]
		NM_000546.5(*TP53*):c.824G > A p.C275Y [2.7]
N-MCL	11	NM_000546.5(*TP53*):c.799C > T p.R267W [5.8]
	58	NM_000546.5(*TP53*):c.916C > T p.R306* [56.9]
	16	NM_000546.5(*TP53*):c.581T > G p.L194R [8.6]
	80	NM_000546.5(*TP53*):c.711G > A p.M237I [84.6]
	3	NM_000546.5(*TP53*):c.475_476insTCCGCG p.R158_A159insVL [15.7]
	9	NM_000546.5(*TP53*):c.578A > G p.H193R [3.7]

3.6. Follow up and outcome

All five patients with L-MCL were alive at last follow up (median, 9.6 months; range, 3.2–26.9). One patient received bendamustine and rituximab (B-R) and one patient received chemotherapy for concurrent breast carcinoma. Three patients did not receive any chemotherapy. Twenty of 21 patients with N-MCL received frontline chemoimmunotherapy. The median follow up time for this group was 11.3 months (range, 1.4–90.5); two (9.5%, 2/21) patients had died at last follow up.

4. Discussion

Mantle cell lymphoma is considered an aggressive mature B-cell lymphoma with relatively short overall survival (OS) of < 3 years and a

Table 3
Karyotype, fluorescent in situ hybridization (FISH) results and percentage of positive cells for t(8;14) rearrangement and common gene mutations in 26 cases of mantle cell lymphoma. Red numbers indicate the L-MCL cases.

Karyotype	simple	complex	simple	complex	complex	complex	simple	simple	complex	simple	normal	normal	NA	NA	normal	NA	simple	simple	normal	NA	simple	NA	NA	simple	NA	normal
FISH t(8;14), %	NA	66%	20%	76%	pos	4%	48%	32%	60%	NA	8%	28%	pos	66%	73%	76%	9%	22%	6%	3%	28%	NA	18%	78%	pos	2%
Pt.ID	1	3	13	18	23	25	2	6	22	7	11	12	21	24	10	19	4	5	8	9	14	15	16	17	20	26
Gene																										
TP53																										
ATM																										
NOTCH1																										
BIRC3																										
CARD11																										
FBXW7																										
SPEN																										

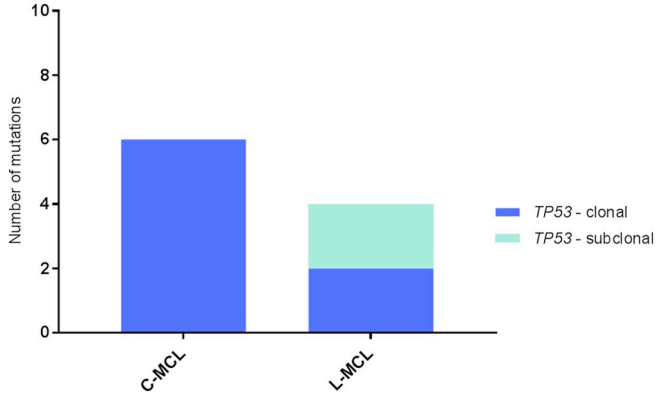

Fig. 2. The chart shows the presence of clonal and subclonal *TP53* mutation in conventional nodal mantle cell lymphoma (N-MCL) and leukemic MCL (L-MCL) patients. Compared to the tumor cell burden in the analyzed specimen, all the mutation in N-MCL patients were clonal while 2 of 4 mutated *TP53* genes in three L-MCL patient were subclonal.

high risk of relapse in most patients [3,25,26]. Patients with MCL are typically treated with intensive chemoimmunotherapy regimens at the time of diagnosis [27,28]. However, indolent forms of MCL have been identified and recently the WHO classification officially recognized two indolent subtypes of MCL, the non-nodal leukemic variant [5,6] and the in situ variant. The recognition of these indolent variants is based on numerous outcome-based and/or molecular studies [12,13,22,29,30]. Patients with indolent forms of MCL have been shown to have significantly better outcome, even without treatment, with long survival duration [12,16,31,32]. The indolent non-nodal variant is more likely to have a simpler karyotype, plasmacytoid morphology, and lack of SOX11 expression [12,15]. The frequency of mutations in highly oncogenic genes such as *TP53*, *ATM*, *NOTCH1* and, *CDNK2A* has been reported to be much lower in the indolent variants of MCL [12,33].

In the current study, we compared the immunophenotypic, cytogenetic, and molecular characteristics of 21 nodal MCL (N-MCL) cases with BM involvement and 5 leukemic, non-nodal MCL (L-MCL) cases. The median age at diagnosis was higher in L-MCL than in N-MCL (71 vs. 64 years). L-MCL was more common in women (60% vs. 26%). SOX11 and CD38 were significantly more often positive in the N-MCL in accord with previous studies [34,35]. Most of L-MCL cases were kappa light chain restricted whereas less than half of N-MCL was kappa restricted. The same result has been observed in other studies [36]. As the usage of *IGV* (both heavy and light chain) genes is biased in MCL [37], the predominance of kappa in L-MCL may indicate differences in antigenic stimulation being involved in the pathogenesis of L-MCL versus N-MCL.

In this study, conventional cytogenetic analysis showed a similar frequency of complex and non-complex karyotypes in both N-MCL and L-MCL. Of note, in 5 cases (including 1 L-MCL) routine karyotyping did not detect the t(11;14) translocation, but the presence of rearrangement was confirmed using FISH in all 5 cases. This discrepancy may be attributable to the lack of growth of lymphoma cells in the 24 hour culture of BM aspirate or PB. Both flow cytometry and FISH analyses showed a higher percentage of BM involvement in L-MCL compared with N-MCL cases. Although the exact mechanism(s) of the higher affinity of L-MCL for BM involvement is incompletely understood, the different expression of BM homing receptors has been postulated to play a role [38]. L-MCL cases showed considerably higher PB lymphocytosis (10.3 k/μL vs. 2.5 k/μL). This difference was commensurate with the higher percentage of BM involvement in L-MCL cases.

TP53 mutations have been shown to be associated with poorer outcome in patients with MCL. In a recently published study, Jain et al. showed that *TP53* aberrations are present in 75% of patients who undergo disease progression on ibrutinib [39]. Ibrutinib-resistant MCL represents a therapeutic challenge and it is important to identify these patients early in the course of disease. An important observation in the current study was the detection of *TP53* mutations in 3 of 5 (60%) cases of L-MCL, with these mutations being subclonal in 2 of 3 mutated cases. Previous studies have shown that the frequency of 17p/*TP53* aberrations is similar between N-MCL and L-MCL; however, genomic complexity and *TP53* aberrations predicted for shorter overall survival (OS) in N-MCL, whereas only genomic complexity was associated with shorter time to first treatment and OS in L-MCL [40]. The reported lack of prognostic significance of *TP53* aberrations in patients with L-MCL, in part, may be explained by the frequent subclonal nature of these mutations in this disease variant. Interestingly, patients with mutated *TP53* in this cohort were slightly older than patients with wild-type *TP53* in contrast to previous studies [21].

While most patients with L-MCL do not need immediate therapeutic intervention and can be observed, it is important to be aware of the high frequency of *TP53* mutations in this disease variant and to monitor these patients for expansion of *TP53* mutated clones as clonal expansion may serve as a surrogate of disease evolution and progression and indicate the need for therapeutic intervention especially as cases with mutated *TP53* may not efficiently respond to the current front-line therapies [21].

In conclusion, we show that *TP53* is commonly mutated in MCL including the indolent non-nodal variant of disease. *TP53* mutations may be clonal or subclonal in nature in the setting of MCL. Although seemingly indolent, cases of L-MCL may harbor subclonal *TP53* mutations which may serve as a useful biomarker for follow-up monitoring and early detection of clonal expansion.

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All authors have contributed to this work. Their contribution is as follows:

Conception and design: AS, SL, JDK.

Provision of study materials or patients: CYO, RKS, CCY, SH, LJM, SL.

Collection and assembly of data: AS, CYO, KPP, ZZ, MJR, JKD, SL.

Data analysis and interpretation: AS, KPP, RKS, CCY, MJR, RL, SL.

Manuscript writing: AS, LJM, SL.

Final approval of manuscript: all authors.

Compliance with ethical standards

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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