Assessment of Immunoglobulin Heavy Variable Gene Usage and Somatic Hypermutation Status in Splenic Marginal Zone Lymphomas Using Next Generation Sequencing

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INTRODUCTION

Splenic marginal zone lymphoma (SMZL) is a rare indolent B-cell neoplasm involving the spleen, bone marrow (BM) and, frequently, blood. Its distinction from similar indolent B-cell malignancies may often be challenging, particularly when diagnosis must be based on the BM findings alone without the support of spleen histology. Prior studies have shown that SMZL exhibit specific immunoglobulin heavy variable gene (IGHV) gene biases which are distinct from other entities and thus ancillary testing could be potentially utilized to aid in the diagnosis or further stratifying this disease. This assessment is, however, often not feasible in the clinical setting as current methods are laborious and not performed in most laboratories. In this study, we explore the utility of next generation sequencing (NGS) for the clinical characterization of IGHV in a cohort of SMZL and compare it to other subtypes of marginal zone lymphomas (MZL) reported in the literature.

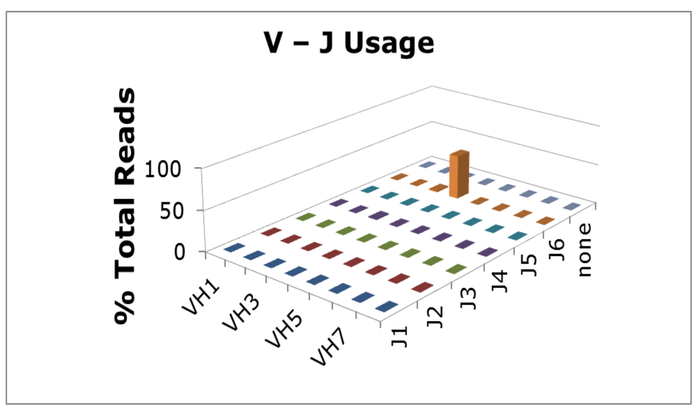
METHODS

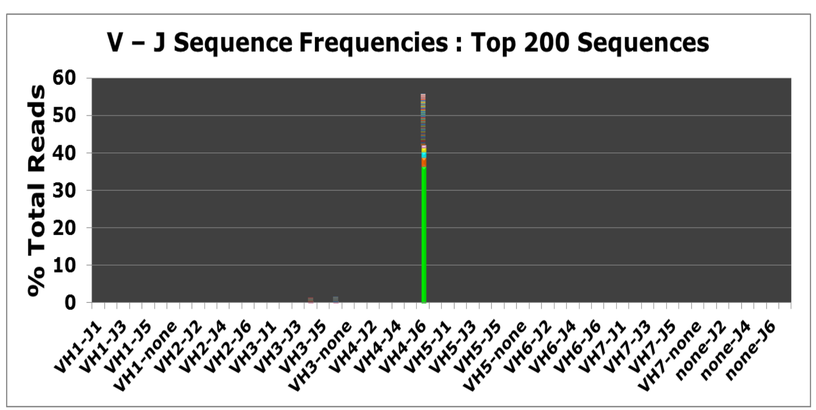
BM samples from patients with an established diagnosis of SMZL and submitted for routine clonality assessment were selected for the study. After establishing the presence of IGH clonality by capillary electrophoresis, the samples were analyzed using an NGS assay targeting IGH-FR1 (Lymphotrack, Invivoscribe) and sequenced by Illumina MiSeq. Data was analyzed using the LymphoTrack IGH-FR1 and Somatic Hypermutation (SHM) software. Clinical and ancillary laboratory data were collected from the electronic medical records.

RESULTS

A total of 20 BM samples were available for analysis (1 sample failed analysis due to low DNA input). Patients included 8 women and 12 men with a median age at diagnosis of 68 years (range: 47 to 87). IGHV families most frequently rearranged were IGHV3 (11/20, 55%) and IGHV4 (6/20, 30%). The IGHV genes most frequently rearranged were IGHV4-34 (4/20, 20%) followed by IGHV3-23 (2/20, 10%), IGHV3-30 (2/20, 10%), IGHV3-33 (2/20, 10%), IGHV3-73 (2/20, 10%) and IGHV1-3 (2/20, 10%). Using a 98% identity cut-off value, 12/20 cases (60%) showed SHM. Review of the literature showed a similar pattern of IGHV usage to other subtypes of MZL.

CASE 10: IGHV4-34/J6 USAGE





SUMMARY OF CASES

Case No.	Sex	Age	IGHV Gene Usage	IGHJ Gene Usage	Somatic Hypermutation Status
1	F	57	V5-51	J4	Unmutated
2	M	65	V3-23	J4	Hypermutated
3	F	80	V3-11	J4	Hypermutated
4	M	63	V4-34	J4	Hypermutated
5	M	47	V3-23	J1	Hypermutated
6	F	70	V4-39	J2	Hypermutated
7	M	71	V4-61	J4	Unmutated
8	M	78	V3-73	J6	Unmutated
9	M	65	V3-9	J5	Hypermutated
10	M	54	V4-34	J6	Hypermutated
11	M	66	V4-34	J4	Hypermutated
12	F	70	V3-33	J4	Hypermutated
13	M	75	V4-34	J4	Unmutated
14	F	62	V1-3	J4	Unmutated
15	F	71	V1-3	J6	Hypermutated
16	F	73	V3-73	J6	Hypermutated
17	M	52	V3-33	J4	Hypermutated
18	M	47	V3-30	J4	Unmutated
19	M	87	V3-30	J6	Unmutated
20	M	77	V3-43	J1	Unmutated

RESULTS

- We confirm that SMZL have a biased IGHV gene usage, which is in keeping with prior literature.
- This usage, however, has significant overlap with other subtypes of MZL considered in the differential diagnosis and therefore does not provide a means of discrimination for diagnostic purposes. This finding however, suggests that the pathogenesis of SMZL may involve epitopes or an antigenic trigger common to other indolent lymphomas.
- Whether particular molecular characteristics of the IG receptors might be associated with clinical outcome, genetic or phenotypic features is an area the deserves further study.

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