These data suggest a pathogenic role for an acquired intracoronary ADAMTS13 deficiency in ACS and indicate that VWF is retained at the site of acute coronary occlusion. In particular, our data support the hypothesis that a decreased ADAMTS13/VWF ratio in the coronary flow favors the presence of highly adhesive VWF multimers that would deposit at the site of a critical stenosis, mediating platelet adhesion and agglutination and, eventually, leading to coronary occlusion. In fact, histologic examination of coronary thrombi aspirated from patients with acute myocardial infarction revealed a prominent co-localization of VWF with platelets.[12,13] These observations are in line with animal models showing that ADAMTS13 deficiency exacerbates VWF-dependent thrombus formation on disrupted plaques, thereby impacting also on the resulting infarct size.[14,15] A surprising finding was the significantly reduced ADAMTS13 activity in coronary blood compared with systemic levels. Although we do not know the reason for this difference, we speculate that it might be explained by local hemodynamic factors (wide flow variations within cardiac chambers followed by low pressure, high velocity intracoronary flow) and/or changes secondary to the acute coronary occlusion (increased proximal coronary flow resistance and intracoronary shear stress because of vascular bed's amputation).

In conclusion, our observations support the hypothesis that a significantly reduced ADAMTS13/VWF ratio in the coronary artery flow plays a pathogenic role in ACS and suggest that transition from laminar to turbulent flow at sites of coronary stenosis further enhances VWF activation and deposition. These events would ultimately sustain platelet adhesion and agglutination, and favor coronary occlusion.

The potential therapeutic implication of this concept, to be clinically tested, would be the local infusion of ADAMTS13 to decrease VWF-mediated platelet adhesion and agglutination at sites of critical coronary stenosis.

There is an Inside *Blood* Commentary on this article in this issue.

Contribution: G.P. designed the study, performed research, analyzed results, and edited the manuscript; L.B. performed research and edited the manuscript; I.S. and A.A. performed research; T.M. and J.A.K.H. analyzed results and edited the manuscript; and L.A. designed the study, analyzed results, and wrote the manuscript.

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To the editor:

First report of *MYD88* ^{L265P} somatic mutation in IgM-associated light-chain amyloidosis

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A mutation in myeloid differentiation factor gene, *MYD88*, leading to constitutive activation of the nuclear factor κB pathway was shown to be oncogenically active in 29% of patients with activated B-cell type diffuse large B-cell lymphoma.[1] The most common somatic variant of *MYD88* mutation is substitution of leucine by proline at position 265 (L265P)[1] because of a single nucleotide change (T→C) in chromosome 3p22.2.[2] Subsequently, *MYD88*^{L265P} was discovered in 86% to 100% of patients with Waldenström macroglobulinemia

(WM)/lymphoplasmacytic lymphoma,[2-4] 10% to 87% of immunoglobulin M (IgM) monoclonal gammopathy of undetermined significance (MGUS),[2-6] 36% to 38% of primary central nervous system lymphoma,[7,8] 6% to 21% of splenic marginal zone lymphoma,[3,4,6] 9% of gastric mucosa associated lymphoid tissue lymphomas, and 2.9% to 4% of those with chronic lymphocytic leukemia.[3,9] *MYD88* is an adaptor protein that drives tumor growth by increased Toll-like receptor and interleukin-1 receptor signaling upon activation of its Toll interleukin-1 receptor domain. This leads to homodimerization and activation of interleukin-1 receptor associated kinase 1 and 4,[1] as well as transforming growth factor-β associated kinase-1.[10]

A risk stratification model in patients with IgM MGUS has predicted an increased 5- and 10-year cumulative incidence of progression to WM or other lymphoproliferative disorders (LPDs) in those harboring $MYD88^{L265P}$ mutation, compared with wild-type variants (5- and 10-year risk of 15% and 45% vs 2% and 14%, respectively).[11] Although primary systemic amyloidosis is associated with clonal plasma cell proliferative disorders or B-cell LPDs,[12] the frequency of an activating *MYD88* mutation has not been studied in this population thus far. In a study by Jiménez et al,[6] patients with light chain (AL) amyloidosis were reported to be negative for $MYD88^{L265P}$.[6] However, isotype of the monoclonal protein was not reported. The objective of our study was to detect the frequency of activating *MYD88* mutation in IgM amyloidosis cases and identify clinicopathologic correlations, if any.

We report data on 15 bone marrow tissue specimens, which were obtained from 14 patients with archival tissue available from the transplant database in Mayo Clinic after approval by the Institutional Review Board. All samples were examined by standard morphology and flow cytometric evaluation of B cells and plasma cells compartments. All available clinical and pathologic data were reviewed.

DNA was extracted from $CD138^+$ or $CD19^+CD138^+$ sorted cells isolated from the bone marrows of IgM amyloidosis patients using the Gentra PureGene DNA Isolation Kit (Qiagen, Valencia, CA). Real-time allele-specific oligonucleotide polymerase chain reaction was performed using qBiomarker Somatic Mutation Assay for *MYD88_85940* (SABiosciences-Qiagen, Hilden, Germany) according to the manufacturer's protocol. The reverse transcription polymerase chain reaction was analyzed using CFX96 real-time thermal cycler (Bio-Rad, Hercules, CA). To obtain a $\Delta\Delta C_t$ range for wild-type alleles, the assay was performed on DNA from 10 $MYD88^{WT}$ controls. The cutoff for wild-type vs mutant *MYD88* was a $\Delta\Delta C_t$ value of 0.003.[10]

Clinical and demographic characteristics of each patient has been summarized in Table 1. Ten out of 14 patients (71%) were positive for the $MYD88^{L265P}$ mutation. Median age of the study population was 60 years (range 48-70 years). Four $MYD88^{L265P}$-positive patients (patients 1, 7, 8, and 10) had a prior diagnosis of WM. Three patients (patients 3, 9, and 13) had biclonal gammopathy on immunofixation. Among $MYD88^{L265P}$-positive patients, bone marrow examination revealed clonal plasma cells in 8 patients (patients 1, 2, 3, 5, 7, 8, 9, and 10), clonal B lymphocytes in 9 patients (patients 1, 2, 4, 5, 6, 7, 8, 9, and 10), and both clonal B lymphocytes and plasma cells in 7 patients (patients 1, 2, 5, 7, 8, 9, and 10). Of note, 9/10 patients with $MYD88^{L265P}$ had clonal B lymphocytes in bone marrow, as opposed to 1/4 patient with $MYD88^{WT}$. Conventional karyotype analysis showed normal karyotype in all patients. Cytogenetic analysis by fluorescent in situ hybridization was done in 8 out of 14 patients. Among $MYD88^{L265P}$-positive patients (5 evaluable patients), 1 patient had trisomy 9, monosomy 13, and deletion of IgH variable region; 1 had normal fluorescent in situ hybridization cytogenetics; and 3 had insufficient plasma cells for analysis. Among $MYD88^{WT}$ patients (3 evaluable patients), 2 patients had t(11;14) and 1 had insufficient plasma cells

Table 1. Clinical and pathologic characteristics of study patients

Patient no.	Age (y)/ sex	*MYD88* L265P mutation	Organs involved	2012 Revised Mayo AL amyloidosis stage†	Monoclonal protein in serum		Urine total protein (g/24 h)	Clonal cells in bone marrow*	OS from diagnosis (mo)	Progression	
					Isotype	g/dL				Y/N	PFS (mo)
1	68/F	Positive	Peripheral nervous system	II	IgM λ	2.4	0.05	Clonal B lymphocytes and clonal plasma cells	109	Y	76
2	70/M	Positive	Peripheral and autonomic nervous system	I	IgM λ	0.9	0.98	Clonal B lymphocytes and clonal plasma cells	43	N	43
3	63/F	Positive	Spleen and kidney	I	IgM λ‡ IgA λ	0.3	8.87	Clonal plasma cells	83	Y	28
4	52/M	Positive	Peripheral and central nervous system	I	IgM κ	0.5	0.08	Clonal B lymphocytes	78‡	Y	67
5	48/F	Positive	Kidney and autonomic nervous system	II	IgM κ	1.5	3.65	Clonal B lymphocytes and clonal plasma cells	62‡	Y	48
6	65/M	Positive	Lungs and lymph node	I	IgM λ	1.4	0.06	Clonal B lymphocytes	41‡	Y	33
7	56/M	Positive	Lymph nodes and soft tissue	I	IgM κ	1.6	0.12	Clonal plasma cells and clonal B lymphocytes	26	N	26
8	65/M	Positive	Kidney	I	IgM κ	2.4	9.59	Clonal plasma cells and clonal B lymphocytes	30‡	N	30
9	60/M	Positive	Kidney	I	IgM κ‡ IgM λ	1.1	1.66	Clonal plasma cells and clonal B lymphocytes	12‡	N	12
10	60/M	Positive	Heart and tongue	III	IgM κ	1.1	0.07	Clonal B lymphocytes and clonal plasma cells	21	N	21
11	62/F	Negative	Kidney	I	IgM κ	0.6	5.90	Clonal plasma cells	104‡	N	104
12	53/M	Negative	Kidney, heart and gastrointestinal tract	III	IgM κ	0.1	34.9	Clonal plasma cells	16	Y	14
13	60/M	Negative	Heart, lymph nodes, and tongue	II	IgM κ‡ IgM λ	0.5	0.20	Clonal plasma cells	120‡	N	120
14	56/M	Negative	Kidney	I	IgM λ	0.9	6.19	Clonal plasma cells and clonal B lymphocytes	55‡	N	55

F, female; M, male.

*Clonality was assessed by immunohistochemistry and flow cytometry from bone marrow specimens.

†Calculated using serum troponin T, N-terminal pro–brain natriuretic peptide, and difference between involved and uninvolved free light chains.

‡Patients alive.

Table 2. Clinical characteristics of patients by *MYD88* mutational status

Clinical characteristics	Overall (n = 14)	*MYD88*^{L265P} (n = 10)	*MYD88*^{WT} (n = 4)
Median age, y (range)	60 (48-70)	61.5 (48-70)	58 (53-62)
Median serum M-spike, g/dL (range)	0.9 (0.1-2.4)	1.15 (0.24-2.4)	0.55 (0.1-0.9)
Cardiac involvement (n)	3	1	2
Peripheral or autonomic neuropathy (n)	4	4	0
Median OS, mo (95% CI)	95.8 (41.2-NR)	83.0 (11.9-108.6)	NR (16.4-NR)
Median PFS	48.2 (27.8-120.3)	43.3 (11.9-75.7)	120.3 (14.0-120.3)

for analysis. Median serum M-spike in *MYD88*^{L265P} and *MYD88*^{WT} patients was 1.15 g/dL (range 0.24-2.3 g/dL) and 0.55 g/dL (range 0.1-0.9 g/dL), respectively. Cardiac involvement was seen in 1 out of 10 patients with *MYD88*^{L265P} and 2 out of 4 patients with *MYD88*^{WT}. Nervous system involvement (peripheral and/or autonomic) was seen in 4 out of 10 patients with *MYD88*^{L265P} and 0 out of 4 patients with *MYD88*^{WT}.

Estimated median-follow up of surviving patients was 77.9 months (95% confidence interval [CI], 26.3-120.3 months). Median overall survival (OS) and progression-free survival (PFS) from diagnosis for the entire cohort was 95.8 months (95% CI, 41.2 to not reached [NR]) and 48.2 months (95% CI, 27.8-120.3), respectively. Median OS in patients with *MYD88*^{L265P} and *MYD88*^{WT} was 83.0 months (95% CI, 11.9-108.6) and NR (95% CI, 16.4-NR), respectively, 5-year OS rates being 60% (95% CI, 24% to 87%) and 75% (95% CI, 24% to 97%), respectively. Median PFS in patients with *MYD88*^{L265P} and *MYD88*^{WT} was 43.3 months (95% CI, 11.9-75.7) and 120.3 months (95% CI, 14.0-120.3), respectively. Statistical significance was not achieved for comparison between the 2 groups, likely because of small sample size. Clinical characteristics and outcomes of the entire cohort has been summarized in Table 2.

IgM-associated AL amyloidosis is a distinct clinical entity, constituting 5% to 7% of all AL amyloidosis cases.[13,14] They are usually characterized by older age at onset, higher incidence of peripheral neuropathy and lymphadenopathy, with no survival difference from non-IgM cases.[14] A study by Landgren and Staudt showing the presence of *MYD88*^{L265P} by Sanger sequencing in 56% of patients with IgM MGUS had demonstrated the presence of clonal plasma cells and clonal lymphocytes in all patients positive for this mutation.[5] In our study, all but 1 *MYD88*^{L265P}-positive patient had clonal B lymphocyte in marrow, likely indicating association of *MYD88*^{L265P} mutation with LPDs. *MYD88*^{L265P}-positive patients had a lower rate of cardiac involvement (1/10; 10%), compared with an expected rate of 32% to 40%[14,15] in patients with IgM amyloidosis. On the other hand, a higher incidence of amyloid neuropathy (4/10; 40%) was seen in these patients. One *MYD88*^{L265P}-positive patient (patient 4) had multiple cranial nerve palsies, an unusual manifestation of amyloidosis. In patients with WM, *MYD88*^{L265P} mutation was shown to be associated with a higher disease burden in bone marrow and peripheral blood, poor response to therapy, and inferior OS.[16,17] It is unclear whether an activating *MYD88* mutation is a driver for increased amyloid deposition by the plasma cell clone and whether presence of these mutations in patients with B-cell LPDs entails an increased risk for development of systemic IgM amyloidosis. Given the ease of detection of *MYD88*^{L265P} mutation, studies should focus on assessing its frequency in larger cohorts of B-cell LPDs and correlating with clinical characteristics, including the development of systemic amyloidosis. A novel oligonucleotide, IMO-8400, which acts by inhibiting activated Toll-like receptor signaling pathway in patients with *MYD88*^{L265P} mutation, is currently being tested in patients with WM/lymphoplasmacytic lymphoma (#NCT02092909) and activated B-cell type diffuse large B-cell lymphoma (#NCT02252146). Preclinical studies in mice have shown antiproliferative activity of inhibitors of *MYD88* dimerization (ST2825),[18] which could create novel therapeutic avenues for IgM amyloidosis in the future.

Contribution: R.C., M.A.G., and A.J.N. designed the study, analyzed the data, wrote the first draft, and approved the final version of the manuscript; M.A.G., S.M.A., A.D., M.Q.L., S.R.H., P.K., F.K.B., and R.L.K. performed patient management, revised the manuscript critically, and participated in final data analysis and approval of the final version of the manuscript; E.M. analyzed data, provided critical review of the manuscript, and approved the final version of the manuscript.

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