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LETTER

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Lack of relationship between mannose-binding lectin variant alleles and risk of arterial thrombosis in Japanese patients with systemic lupus erythematosus

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To the Editor:

Large increases in mortality related to premature atherosclerosis and cardiovascular disease have been reported in patients with systemic lupus erythematosus (SLE). Factors such as inflammation in the blood vessels and steroid intake may contribute to this phenomenon.

Mannose-binding lectin (MBL) is a serum protein that binds to various organisms and exerts an opsonin effect against various microorganisms. Mannose-binding lectin also mediates lectin-dependent activation of the complement pathway. There are three single nucleotide polymorphisms on exon 1 (codons 52, 54, and 57) of the MBL gene, and possession of any of the minority alleles (collectively designated as allele O; the wild allele is designated allele A) cause significant reduction of the serum MBL concentration. It has been reported that MBL deficiency increases risk of infection. A number of studies in different ethnic groups have also indicated that the presence of the MBL minority alleles influences susceptibility to SLE.[1] Recently, it has been shown that MBL deficiency is associated with the development of atherosclerosis in the general population.[2] Furthermore, Øhlenschlæger et al. have shown that among patients with SLE, the probability of having arterial thromboses is significantly higher in patients with two MBL variant alleles (O/O genotype) than in other patients.[3]

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In a recent study, we investigated the relationships between various aspects of SLE and MBL genotypes or serum MBL concentrations.[4] Here, we studied the relationship between MBL genotypes and arterial complications in 142 Japanese SLE patients. The MBL genotypes were assessed by the restriction fragment length polymorphism method, as described previously.[4] Arterial and venous thromboses were confirmed by appropriate diagnostic methods.

The total follow-up period was 1916 patient-years, and the median disease duration was 13.3 years. One of nine SLE patients with O/O genotype and 7 of 133 patients with other genotypes had a history of arterial thromboses (Table 1a). In our patients, deficiency of MBL was not statistically associated with arterial thrombosis ($P = 0.4159$), or venous thrombosis ($P = 0.5592$). Having O alleles (genotypes A/O and O/O) also did not increase the risk of arterial or venous thromboses ($P > 0.9999$). Next, we examined the relationships between other possible risk factors and history of thromboses (Table 1b). We found male sex ($P = 0.0059$), elevation of total cholesterol level at sampling ($P = 0.0075$), and age at diagnosis of SLE ($P = 0.0141$) to be significantly associated with histories of arterial thromboses in SLE patients. These factors may be related to enhanced atherosclerosis in these patients. Furthermore, possession of anticardiolipin antibody ($P = 0.0141$) and/or lupus anticoagulant ($P = 0.0059$) were associated with a history of arterial thromboses, as expected. Since increased activity of SLE may lead to more vascular damage and increased usage of immunosuppressants and steroids, we investigated associations between a history of arterial thromboses and clinical characteristics of SLE that may reflect disease severity. However, we did not find significant relationships among them (data not shown).

Øhlenschlæger et al.[3] suggested that the reasons for association between MBL deficiency and thrombotic events may be (1) increased risk of infection, in particular *Chlamydia pneumoniae*, which is reported to cause cardiovascular diseases, or (2) decreased clearance of apoptotic and damaged host cells from vessels. On the other hand, other studies have indicated that complement activation caused by MBL may lead to organ damage. In addition, it is reported

Table 1a. Incidence of arterial or venous thromboses among 142 Japanese patients with systemic lupus erythematosus categorized by mannose binding lectin genotypes

	A/A (n = 80)	A/O (n = 53)	O/O (n = 9)	Odds ratio O/O vs A/A + A/O (95% CI)	P value
Arterial thrombosis	5 (6.3%)	2 (3.8%)	1 (11.1%)	2.25 (0.25–20.59)	0.4159
Venous thrombosis	7 (8.8%)	4 (7.5%)	1 (11.1%)	1.39 (0.16–12.12)	0.5592

A, mannose-binding lectin gene majority allele; O, mannose-binding lectin gene minority alleles; CI, confidence interval
P values by Fisher's exact test

Table 1b. Relationship between history of arterial thromboses and probable risk factors

	Arterial thrombosis (+) (n = 8)	Arterial thrombosis (–) (n = 134)	Odds ratio (95% CI)	P value
MBL genotype O/O	1 (12.5%)	8 (6.0%)	2.25 (0.25–20.59)	0.4159
IgG anticardiolipin antibody	4 (50%)	16 (11.9%)	7.38 (1.68–32.43)	0.0141
Lupus anticoagulant	4 (50%)	12 (9.0%)	10.17 (2.25–45.91)	0.0059
Male sex	4 (50%)	12 (9.0%)	10.17 (2.25–45.91)	0.0059
Total cholesterol >2.4 g/l	4 (50%)	13 (9.7%)	9.31 (2.08–41.69)	0.0075
Age at diagnosis > 45 years	4 (50%)	16 (11.9%)	7.38 (1.68–32.43)	0.0141

A, mannose-binding lectin gene majority allele; O, mannose-binding lectin gene minority alleles; CI, confidence interval
P values by Fisher's exact test

that in patients with type I diabetes, serum MBL levels were higher in patients with nephropathy or cardiovascular disease.[5]

Thus, while we were unable to confirm the relationship between MBL deficiency and arterial thrombosis, whether there is such a relationship or not needs to be elucidated, since typing the MBL genotype is relatively easy and would greatly aid in the management of SLE patients if such a relationship does exist.

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