The Association between Mycoplasma Infections and Atherosclerosis: Myth or Clinical Reality?

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Atherosclerosis is a multifactorial disease with growing prevalence worldwide and is currently considered an immune mediated inflammatory disease [1]. Several autoantigens have been identified in atherosclerosis: heat-shock proteins, β2-glycoprotein-I, and oxidized low density lipoproteins. Increased inflammation in the atherosclerotic plaque is associated with increased plaque vulnerability [2].

Tissue damage due to infections, exposure to autoantigens, molecular mimicry, bystander activation of autoreactive immune T cells, and persistent infections may trigger autoimmunity [3]. Therefore, it is plausible that some infectious agents may trigger or aggravate immune mediated atherosclerosis. An association between infections and atherosclerosis was first demonstrated in 1978 [4]. Several infectious agents have been suggested as possible contributors to the acceleration of the atherosclerosis process [5]. Espinola-Klein and colleagues [6] reported that elevated antibody titers against *Chlamydia pneumoniae*, *Helicobacter pylori*, herpes simplex virus-2 and cytomegalovirus are associated with more advanced atherosclerosis, after adjustment for other risk factors. Although the association between some infectious agents and atherosclerosis are supported by several studies, a controversy still exists as to the possible role of *Mycoplasma pneumoniae* in induction and acceleration of atherosclerosis. Moreover, it is unknown whether an immune reaction against *M. pneumoniae* is associated with an adverse prognosis.

Animal model studies with *M. pneumoniae* have also yielded conflicting results. Intraperitoneal inoculation of *C. pneumoniae* and *M. pneumoniae,* or both, aggravated atherosclerosis in apolipoprotein-E knockout mice fed a cholesterol-enriched diet [7]. Nevertheless, in a rabbit model, *M. pneumoniae* was found to be associated with periaortitis, but not atherosclerotic lesions [8].

Using an electron microscopy apparatus, Higuchi et al. [2] were probably the first to detect *C. pneumoniae* and *M. pneumoniae* in thrombosed ruptured atheromas in humans. It has been suggested that large amounts of *C. pneumoniae* and *M. pneumoniae* in the plaque contribute to its vulnerability [9]. In 2006, Weiss and colleagues [5] evaluated the presence of *M. pneumoniae* (by polymerase chain reaction) in atherosclerotic plaques of the carotid artery, in apparently healthy greater saphenous veins and in circulating leukocytes. Samples were collected from 36 patients who had carotid artery stenosis and 25 without evidence of marked carotid artery stenosis. No association was found linking the presence of *M. pneumoniae* DNA in leukocytes, carotid plaques and veins with inflammatory markers [5]. In addition, Reszka et al. [10] found similar detection rates of *M. pneumoniae* in the aortic wall of patients with three-vessel coronary artery disease and in those who had normal coronary angiography and needed aortic valve replacement.

Momiyama et al. [8] used the complement fixation test to evaluate seropositivity for *C. pneumoniae* and *M. pneumoniae* in 396 patients with coronary artery disease, and 153 patients without coronary artery disease. Anti-*M. pneumoniae* antibody titer ≥ 1/8 and ≥ 1/16 were significantly more common in patients with coronary artery disease, although no difference was found for a titer of ≥ 1/4 (also considered seropositive) [8]. In a multivariant analysis, *M. pneumoniae* (titer of ≥ 1/8) was found to be associated with coronary artery disease only in patients seropositive for *C. pneumoniae* [8]. In addition, Goyal et al. [11] reported that combined seropositivity with *M. pneumoniae* and *C. pneumoniae* are more common in patients with coronary heart disease and a history of myocardial infarction. Reunanen et al. [12] found that the incidence of coronary artery disease in men without a prior history of heart disease significantly increased in those with the highest quartiles of antibody levels against *M. pneumoniae*, compared to men with antibody titers in the lowest quartile. Nevertheless, the presence of anti-*M. pneumoniae* antibodies did not demonstrate prognostic significance in men with a positive history of heart disease [12]. Maia and collaborators [4] reported a lack of statistical significance when values of anti-*M. pneumoniae* IgG

Ig = immunoglobulin

levels of patients with acute coronary syndrome were compared with the antibody titer of patients with chronic coronary disease and controls. Additionally, patients with chronic atherosclerosis had a similar antibody titer compared with controls [4].

In the current issue of *IMAJ*, Barski et al. [13], using an agglutination test or enzyme-linked immunosorbent assay, measured the anti-mycoplasmal antibodies in 150 patients with coronary heart disease and in 98 healthy blood donors, noting that patients with coronary heart disease do not have a higher rate of seropositive results for *M. pneumoniae, Ureaplasma urealyticum, M. fermentans, and M. hominis* compared with the controls. Barski et al. [13] provide the first systemic evaluations of the association between *Ureaplasma urealyticum, M. fermentans and M. hominis* – and coronary heart disease. The authors carefully noted that the results did not exclude the association between Mycoplasma infections and atherosclerosis and suggest that the intracellular localization may be associated with less pronounced humoral activation and antibody production.

Barski et al. [13] are in agreement with Espinola-Klein et al. [6] who found no correlation between the extent of atherosclerosis and seropositivity for *M. pneumoniae* IgG and IgA. Nevertheless, they reported a higher mortality in patients who were seropositive for more pathogens (including *M. pneumoniae* and others) and thus subject to a higher infectious burden [6]. In another study, Espinola-Klein et al. [14] reported an association between seropositivity for *M. pneumoniae* IgA and progression of carotid atherosclerosis in a univariant analysis. However, significance was obliterated following adjustment for other conventional risk factors.

Importantly, definite conclusions regarding the role of Mycoplasma infections in atherosclerosis and heart disease is limited by the different methodologies for evaluating infection (namely PCR, in situ hybridization, electron microscopy techniques, ELISA, indirect immunofluorescence, and complement fixation test), and different criteria for defining serologic positivity. It should be emphasized that anti-*M. pneumoniae* IgG measurement via different ELISA kits have a high sensitivity (75–83%), whereas measurement of IgM is highly dependent on the type of kit used (16–58% sensitivity) [15]. Csángó and and co-authors [16] also reported a wide range of detection frequency of anti-*M. pneumoniae* IgM (2.8–16%) and IgA (22.8–68.5%) in healthy blood donors when different kits were used, and concluded that the use of certain kits may lead to over-diagnosis. Moreover, no association was observed in small studies between anti-*M. pneumoniae* IgG and positive PCR test of atherosclerotic plaques and circulating leukocytes [5].

In conclusion, it seems unlikely that a single infectious agent is associated with atherosclerosis, coronary artery diseases and cardiovascular events [6]. Uncertainty still remains regarding the possible contribution of Mycoplasma infections to the process of atherosclerosis, especially in the presence of a high infectious burden. Future research should focus on establishing standards of measurements for detecting Mycoplasma infections, and evaluating the consequences of Mycoplasma co-infection with other specific pathogens.

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PCR = polymerase chain reaction
ELISA = enzyme-linked immunosorbent assay

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