Atherosclerosis: Lipid Infiltration or Chlamydia pneumoniae Infection?

To the Editor:

The figure that appears in the article by Libby et al., as well as on the cover of the same edition, shows atherosclerosis as a lipid infiltrative type of lesion with primary attachment and infiltration of monocyte/macrophage foam cells.1 Pathological studies, however, show additional features, such as the foam cell component consisting of a combination of macrophages and intimal smooth muscle cells, and containing not only lipid but Chlamydia pneumoniae (Cp) organisms as well. Another feature is fragmentation and necrosis of Cp-infected intimal smooth muscle cells, with a monocye/macrophage response showing engulfment not only of lipid, but also of muscle fragments and Cp organisms.2 When examined with an electron microscope, the central lipid-rich core consists mainly of a colony of lipohophilic Cp organisms, not lipids as previously thought.2 This type of arterial lesion seems to occur even in patients with cholesterol disorders. The association of the hypercholesterolemia and premature severe atherosclerosis in homozygous familial hypercholesterolemia (HFH) forms the strongest basis on which cholesterol is implicated in the atherosclerotic process. Patients with this rare, autosomal, codominantly inherited disorder are characterized by markedly elevated levels of plasma low-density lipoprotein cholesterol, tendon xanthomata, and severe, premature atherosclerosis, particularly coronary artery disease. If untreated, the majority of patients with this disorder die from accelerated atherosclerosis before the age of 30 years. We recently examined atherosclerotic lesions of a 16-year-old female with HFH who died as a result of severe premature atherosclerosis.3 Somewhat surprisingly, the atherosclerotic lesions were not lipid infiltrative in nature, as one would expect, but showed the same pathological features as conventional atherosclerosis, with large numbers of Cp organisms.4 Perhaps cholesterol is capable of enhancing the growth of Cp organisms, as lipid is not only produced by Chlamydia organisms but is also involved in Chlamydia nutrition, metabolism, and cell wall formation. Hypercholesterolemia is a symptom of HFH, the primary disorder that is a defect of the cholesterol receptors characterized by decreased cellular utilization of cholesterol.4 Relatively recently, it has been discovered that cholesterol plays a cellular role in mechanisms of transcription and posttranscription events that affect meiosis, apoptosis, developmental patterning, protein cleavage, and protein degradation of cells.5 Perhaps defects in regulatory cholesterol-related events play a role. Whatever the association between lipid and this disease, pathological studies suggest human atherosclerosis is an infective Chlamydia lesion, rather than a lipid infiltrative type lesion.

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Response

We thank Dr Shor for his intriguing comments regarding the role of Chlamydia pneumoniae in atherosclerosis. We agree that strong evidence links products of Chlamydia pneumoniae with atherogenesis and lipid metabolism by macrophages. Indeed, our own data support a novel role for Chlamydia pneumoniae heat shock protein as a pro-inflammatory mediator and have defined the involvement of CD14 in the molecular signaling of this pathway.1,2 Kalayoglu, in Byrne’s laboratory, found that the chlamydial heat shock protein-60 promotes cellular oxidation of low-density lipoprotein,3 and that chlamydial endotoxin induces macrophage foam cell formation.4 This work, as well as related findings from other groups, provides a firm pathophysiological foundation for potential involvement of Chlamydia in atherosclerosis and local lipoprotein metabolism within atheroma.

Despite this fascinating basic science, translation to the clinic remains problematic. The recent preliminary reports of the Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders (WIZARD) study results showed no effect of 12 weeks of azithromycin treatment in survivors of myocardial infarction.5 These negative clinical trials in no way refute the hypothesis that Chlamydia can potentiate atherogenesis, as Gieffers et al found that azithromycin cannot eradicate intracellular Chlamydia pneumoniae in human monocyte/macrophages.6 The ongoing Azithromycin and Coronary Events Study (ACES) is evaluating longer term treatment with azithromycin (12 months) in survivors of myocardial infarction. The PRavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE-IT) study will assess the effects of the fluoroquinolone antibiotic gatifloxin in patients with acute coronary syndromes.

We currently view the evidence for a role of Chlamydia in atherosclerosis as follows:

1) Seroepidemiological evidence supporting a role for Chlamydia in atherosclerosis and coronary events remains unconvincing.
2) A concordant data set suggests that human atherosclerotic plaques may contain Chlamydia pneumoniae, in agreement with Dr Shor’s observations, but the prevalence of such infection may exhibit regional, racial, and age-related differences.
3) Plausible biological mechanisms for a potentiation of atherogenesis by infection with Chlamydia pneumoniae exist.
4) Some animal experiments have shown potentiation of atherogenesis by infection with Chlamydia pneumoniae.
5) Clinical trials have not yet validated the use of antibiotics in secondary prevention of coronary artery disease.

In conclusion, we share Dr Shor’s fascination with the possible role of Chlamydia pneumoniae in atherogenesis. We believe that chlamydial infection, if present, might potentiate atherosclerosis, acting in concert with risk factors such as disorders of lipid metabolism, rather than as a sole etiologic agent in the vast majority of cases.

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