Letters to the Editor are welcomed. They may report new clinical or laboratory observations and new developments in medical care or may contain comments on recent contents of the Journal. *They will be published, if found suitable, as space permits. Like other material submitted for publication, letters must be typewritten, double-spaced, and must not exceed* ***two*** *typewritten pages in length. No more than five references and one figure or table may be used. See "Information for Authors" for format of references, tables, and figures. Editing, possible abridgment, and acceptance remain the prerogative of the Editors.*

Mechanisms Other Than Atherosclerosis in the Partnership Between *Chlamydia* and Stroke

To the Editor: I read with great interest the article entitled "Association of *Chlamydia pneumonia* serology and ischemic stroke" by Hasan[1] in the May 2011 issue of the *Journal*. The study focuses on the long debated issue of *Chlamydia pneumonia* infection and vascular events, and the result elegantly solidifies the connection. However, I would like to enrich this article by further discussing the potential mechanisms behind the phenomenon, in addition to atherosclerosis.

Chlamydial infection has been linked to vascular accidents such as coronary artery disease and myocardial infarction, by large-scale epidemiologic works since late in the 1980s.[2] Though the relationship is not consistently confirmed in subsequent prospective studies, stroke, especially the ischemic type, is also found to possess a strong association with a recent chlamydial infection. The proposed mechanisms include atherosclerosis, vasculitis from persistent infection and transient anti-phospholipid antibody formation during acute infection. *C. pneumoniae* infection contributes to atherosclerosis directly through infection of atheromatous tissues with increasing platelet adhesion, as well as recruitment of leukocytes, and indirectly, by stimulated cytokine production from atheroma-indwelling macrophages, leading to ongoing inflammation and weakening of the fibrous cap.[3] However, a recent discovery that chlamydial infection is associated with certain rheumatologic diseases (rheumatoid arthritis, lupus erythematosus, ANCA-associated glomerulonephritis) also suggests the possibility that bacterial infection may trigger host autoimmunity and result in a prothrombotic status.[4] Elkind et al, in their large-scale studies of infectious serologies with vascular event incidence, have found that a combination profile of 5 common pathogen infections (*Chlamydia pneumoniae*, *Helicobacter pylori*, herpes simplex virus type I and II, cytomegalovirus) significantly increases the overall risk of ischemic stroke.[5] This finding shows that chlamydia infection may also be part of the infection burden that, on the whole, signifies persistent inflammation and tendency for a vascular thrombotic event in the future. Thus, while Hasan focuses on atherosclerosis as one mechanism from chlamydial infection to a vascular event such as stroke, I think we might be able to gain another vision of this supposed viral complication if these aforementioned pathways are put into consideration.

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Chlamydia pneumonia and Stroke

To the Editor: The association between stroke and *Chlamydia pneumonia* infections is still unclear. Proposed mechanisms behind the risk of stroke in patients with acute and chronic infections are multiple and variable and include vasculitis, increased platelet adhesiveness, increased leukocyte recruitment, cytokines production and a high association with rheumatologic diseases. Other mechanisms involve matrix metalloproteinase-9 expression which is associated with the presence of *Chlamydia pneumonia* in human coronary atherosclerosis.[1] Matrix metalloproteinases are prevalent in the arterial wall throughout the arterial system and are associated with local plaque destabilization.[2] Chronic *Chlamydia pneumoniae* infection may promote coronary artery disease in humans through enhancing secretion of interleukin-4,[3] which augments cholesterol esterification in macrophages leading to profound increment of the atherogenic process.[4] Also *Chlamydia pneumonia* induces macrophage-derived foam cell formation by up-regulating cholesterol acyltransferase (acyl-coenzyme A and cholesterol acyltransferase)[5]; those enzymes regulate cholesterol storage as cholesterol ester in the vascular walls and many other organs.[6] Also chronic *C. pneumoniae* infection has been associated with increased triglyceride and decreased high-density lipoproteins.[7]

Elkind et al defined infectious burden as the cumulative life-course exposure to infectious agents that elicit strong

inflammatory responses[8]; this postulation means a combined added effect of multiple microorganism carries more risk of inflammation and stroke risk thereafter. Hirono et al found that infected vascular cells by combination of *C. pneumonia* and adenovirus encoding human heat shock proteins [HSP60] result in a significant increase in [HSP60] proteins which were involved in the regulation of cell cycle progression and cell proliferation. Overexpression of [HSP60] in infected vascular cells leads to the proliferation of vascular smooth muscle cells.[9]

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Liver Biopsy in Hepatocellular Cancer: How Closely Do We Adhere to the Guidelines?

To the Editor: Hepatocellular cancer (HCC) is one of the most dreaded complications of cirrhosis. With the advent of dynamic imaging like triphasic CT scans and MRI with gadoxetate disodium, the diagnosis of HCC can be made with certainty in most cases within a cirrhotic liver. In November 2005, the American Association of Study of Liver Diseases (AASLD) issued guidelines stating that if a hepatic lesion within a cirrhotic liver is greater than 2 cm in diameter and shows the characteristic features of HCC (ie, arterial hypervascularity and wash out in the early or delayed venous phase), only a single imaging modality is required for diagnosis.[1] This can be demonstrated on triphasic CT scan or MRI with gadolinium injection. To assess our adherence to the AASLD guidelines regarding use of liver biopsy in HCC, we reviewed the records of all patients with a diagnosis of HCC over a period of 5 years from January 2006 to December 2010.

Over this period of 5 years, there were 48 patients who were diagnosed with HCC. The mean age was 63.0 ± 11.9 years. Of these 48 patients, 32 patients had a liver biopsy in order to further characterize their liver lesions. Of these 32 patients, 18 patients did not meet the AASLD criteria to pursue a liver biopsy in order establish the diagnosis of HCC.

This study highlights that, in spite of the risk and complications associated with liver biopsy, including a theoretical risk of tumor seeding along the needle tract and the risk of recurrence of tumor following a liver transplantation, there was a significant percentage of nonadherence to AASLD guidelines to evaluate lesions ≤2 cm within a cirrhotic liver.

We suspect this finding is not unique to our institution and highlights the importance of renewing efforts to improve education within the medical community in order to avoid unnecessary and potentially harmful diagnostic procedures.

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Atrial Fibrillation in Cancer Patients: An Underrecognized Condition

To the Editor: Cancer remains the second most common cause of death in the United States while atrial fibrillation (AF) is the most common arrhythmia in elderly people. Though there are several proposed risk factors for AF, it is unclear if cancer is a risk factor for AF or vice-versa. Recent data suggest that AF may be an inflammatory complication resulting from initiation of an inflammatory response to any inciting agent such as stress, surgery, and infection.[1] Chung et al analyzed the association between cancer, AF and inflammatory state and reported that atrial arrhythmias were significantly more common in patients with a history of malignancy ([18.3%] vs [5.6%], $P = 0.018$).[1] A statistically significant elevation of serum levels of C-reactive protein was

found in patients with AF and in patients with a history of cancer.[2] However, cancer was not found to be an independent predictor of atrial arrhythmias in multivariable analysis. Walsh et al reported that AF correlated with worse two-year survival ($P = 0.04$) in 175 cancer patients. However, in a Cox regression analysis AF was not found to be an independent predictor of survival.[3] Cancer progression causing extreme inflammatory stress, surgical treatments especially intrathoracic procedures, chemo- and radiation therapies are all potential inciting factors for AF.[4] Chemotherapeutic agents such as cytotoxic agents and targeted therapies including monoclonal antibodies that target tyrosine kinase receptors, anti-angiogenic drugs, small molecule tyrosine kinase inhibitors and chemoprevention agents such as cyclooxygenase-2 inhibitors and high-dose corticosteroids affect the cardiovascular system and can contribute to AF.[5] Additional reasons such as persistent pain, hypoxia, tachycardia, electrolyte abnormalities and malnourishment which are common manifestations in cancer patients can cause several autonomic, metabolic and endocrine abnormalities contributing to AF. Management of AF also remains a challenge in cancer patients due to increased risk of bleeding, unpredictable anticoagulant response and lack of controlled studies in this population. There are no specific American College of Cardiology/American Heart Association/European Society of Cardiology guidelines to date for the management of AF in this unique set of patients. The incidence of AF in cancer patients remains underrecognized. There is a need for more epidemiological studies showing the association between AF and various types of cancers to establish specific cancers at risk for AF and optimize treatment and preventive strategies for favorable patient outcome.

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