What Can Lipids in Anti-neutrophil Cytoplasmic Antibody-associated Vasculitis Tell Us?

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Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are systemic inflammatory autoimmune diseases with diverse clinical manifestations mainly involving small-sized blood vessels. Our understanding of AAV have significantly improved since the first description of a patient now suspected of granulomatosis with polyangiitis in 1931 by Klinger [1]. Association with ANCA was first reported by van der Woude et al. [2] in 1985. While its value of ANCA in diagnosis of AAV is well accepted [3], its association with disease activity is controversial [4].

The 1990 American College of Rheumatology classification criteria, 2007 European Medicine Agency algorithm for the classification of AAV, and revised 2012 Chapel Hill consensus conference nomenclature of vasculitides aids us in the diagnosis of AAV. Clinical features as well as imaging and laboratory tests and most importantly histology make up the diagnosis. But besides the clinical manifestations, other aspects of the disease have very limited impact on assessment of disease activity. The international Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group have endorsed the Birmingham Vasculitis Activity Score (BVAS) for assessment of disease activity in AAV [5]. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ANCA, B-lymphocytes, and gamma-globulins has been used in randomized clinical trials to assess disease activity, but their validity remains unclear [6].

Efforts to identify biomarkers for AAV have suggested neutrophil microparticle, neutrophil extracellular traps, urinary MCP-1, urinary soluble CD16, CXCL13, matrix

metalloproteinase-3, tissue inhibitor of metalloproteinases-1, S100A8/A9, mobilitygroupbox-1 protein, typical damage-associated molecular pattern protein, C3a, C5a, and soluble C5b-9 as potential candidates [7]. Other possible candidate includes neutrophil to lymphocyte ratio [8], platelet to lymphocyte ratio [9], hepcidin [10], IL-6 [11], d-dimer [12], vitamin D levels [13], soluble lectin-like oxidized low-density lipoprotein receptor 1 [14], mannose-binding lectin levels [15], and lipid levels [16]. But there is no validated biomarker for assessment of disease activity in AAV.

The outcomes of AAV have greatly improved with the use of glucocorticoids and cyclophosphamides and now with rituximab. But it can show frequent relapses and adverse events from therapies especially with glucocorticoids can cause significant morbidities. Comorbidities are also an important aspect of management of AAV. Increased cardiovascular risk in patients with AAV is well recognized warranting active management [17].

Wallace et al. [16] showed temporal relationship between change in lipid levels and remission induction in a post hoc analysis of the Rituximab for ANCA-Associated Vasculitis (RAVE) trial. They concluded that the assessment for cardiovascular risk using lipid profiles in the initial phase after the diagnosis of AAV before remission induction may not accurately reflect the true risk. Patients with AAV are at increased risk for cardiovascular disease and timing of lipid profile assessment may have a role in its active management. It also implies that lipid profile decreases in active disease state with active inflammation which is consistent with findings in other inflammatory

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rheumatic diseases.

Ahn et al. [18] also demonstrated relationship between lipid profile and disease activity in AAV in a cross-sectional study. It was irrespective of treatment of corticosteroids and immunosuppressant and apolipoprotein A1 (apoA1) showed the most significant correlation. ApoA1 is a known acute phase reactant and its correlation with acute coronary syndrome in high risk population have been demonstrated [19]. Apolipoprotein B (apoB) to apoA1 ratio has been shown to correlate with cardiovascular risk [20].

Multiple studies show correlation between lipid profiles and disease activity in AAV. The phenomenon may not be specific to AAV, but rather a response to persistent active inflammation that can be seen in autoimmune inflammatory diseases. Similar results has been shown in other inflammatory rheumatic diseases. Decrease levels of total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) with active rheumatoid arthritis (RA) and their increase after decrease in RA disease activity with treatment have been observed correlating with cardiovascular risk, hence the lipid paradox [21]. The correlation between lipid profiles and CRP has also been observed [22]. Nevertheless, we are lacking valid biomarkers of disease activity in AAV and it would be valuable if lipid profiles, which are routinely assessed, can provide information on AAV disease activity.

Management of cardiovascular risk is an important part of AAV management. Lifestyle modification including smoking cessation and management of blood pressure and dyslipidemia is recommended. Assessment of dyslipidemia is an important part of cardiovascular risk assessment and it has been shown that the results may be altered with AAV disease activity. Using lipid profile in active stage of AAV disease activity may underestimate cardiovascular risk and undermine efforts for active management.

Non-HDL cholesterol based assessment are generally accepted for cardiovascular risk stratification in general population. However, dysfunctional proinflammatory HDL has been suggested as a key component of increased cardiovascular risk in autoimmune inflammatory diseases such as systemic lupus erythematosus (SLE) [23]. Ahn et al. [18] have shown that apoA1, an important component of HDL, is significantly associated with AAV disease activity and it will be interesting to see how it correlates with cardiovascular diseases.

Lipid profile should be routinely assessed in patients

with AAV and it can provide valuable information. Evidence show that avoiding the use of lipid profile during active inflammatory phase of AAV is advisable when interpreting the results for cardiovascular risk assessment. It may in turn suggest that lipid profile can add information in assessing disease activity in AAV.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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