LETTERS TO THE EDITOR

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Persistent Moderate-to-High Level Isolated Anticardiolipin Antibody IgA or Anti-B_2-Glycoprotein-I IgA Isotypes: Do They Have Any Clinical Relevance?

Persistan Orta-Yüksek Seviyede Izole Anti-kardiyolipin Antikoru IgA veya Anti- β_2-glikoprotein-I IgA Izotiplerinin Herhangi Bir Klinik Önemi Var Mı?

Keleşoğlu Dinçer A.B. et al: Isolated IgA Antiphospholipid Antibody

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Dear Editor,

The 2023 ACR/EULAR Antiphospholipid Syndrome (APS) classification criteria include persistently positive lupus anticoagulant (LA), anticardiolipin antibody (aCL) IgG/IgM, and/or anti-β2-glycoprotein-I (aβ2GPI) antibody IgG/IgM [1,2]. However, aCL/aβ2GPI IgA is not part of the classification criteria due to: a) limited evidence for its thrombogenic potential; b) unclear contribution to APS classification [3]; and c) the lack of assay standardization [3,4].

Since the clinical relevance of IgA isotype is not well determined, and is rarely encountered, our goal was to retrospectively describe the demographic, clinical, and laboratory characteristics of patients with persistent (two or more occasions 12 weeks apart), moderate-to-high level (> 40 enzyme-linked immunosorbent assay [ELISA] Units), and isolated aCL IgA and/or aβ2GPI IgA positivity.

Among 578 patients evaluated for "antiphospholipid antibody (aPL)-positivity", we identified only 10 (1.7%) patients with moderate-to-high level of isolated aCL IgA or aβGPI IgA positivity (Female: 9; White: 4, Mean age: 47.5 ± 15.4 years). No patients had a history of thrombosis, pregnancy morbidity, or non-thrombotic complications. Only one patient with isolated aCL IgA had livedo reticularis, no patients had simultaneous aCL IgA and aβ2GPI IgA positivity. During the mean prospective follow-up of 7.5± 5.9 years since the initial aPL positivity, 3/10 (30%) had disappearance of aPL.

The prevalence of isolated IgA aCL/aβ2GPI in patients with or without other systemic autoimmune diseases but presenting with aPL-related manifestations varies widely between studies due to: a) different ethical distribution of patients; b) variability in the cut-off levels of IgA. In our cohort of 578 patients evaluated for aPL-positivity, only 1.7% were persistently positive for isolated aPL IgA, supporting previous studies that the prevalence of isolated aCL/aβ2GPI IgA positivity is extremely low.

In 1995, for the first time Pierangeli *et al.* demonstrated in vivo that IgA aCL has a role in thrombosis formation [5]. When the pathogenicity of aβ2GPI IgA was evaluated in a mouse model of thrombosis, the mice inoculated with purified aβ2GPI IgA had significantly larger thrombi and tissue factor expression [6]. Although a limited number of small clinical studies, especially in SLE, showed that IgA isotype is associated with thrombosis, pregnancy morbidity, and microvascular manifestations, other studies, did not show any association between IgA aPL and aPL-related clinical manifestations, and argued against the diagnostic utility of adding aPL IgA to standard testing [7-9]. Based on the available data, we agree that routine measurement of IgA does not improve the operative characteristics of aCL and aβ2GPI IgG/M.

Limitations of our study include small number of patients (however, isolated IgA positivity is rare), and the lack of a comparison group (thus, we prefer to report our results in a descriptive

fashion). Despite these limitations, we believe that a major strength of our study is inclusion of patients with persistent moderate-to-high titers of aCL/aβ2GPI IgA with confirmed negative aCL/aβ2GPI IgG/M and LA results.

To conclude, based on our small cohort, there was no association between isolated aCL/aβ2GPI IgA positivity and aPL-related clinical manifestations. Large-scale mechanistic and clinical studies are needed to better define the clinical relevance of isolated IgA positivity.

Conflict of Interest: None to declare

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