LETTER TO THE EDITOR

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Persistent Moderate-to-High Levels of Isolated Anticardiolipin Antibody IgA or Anti-β_2-Glycoprotein-I IgA Isotypes: Do They Have Any Clinical Relevance?

Persistan Orta-Yüksek Seviyede İzole Anti-Kardiyolipin Antikoru IgA veya Anti-β_2-Glikoprotein-I IgA İzotiplerinin Herhangi Bir Klinik Önemi Var mı?

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To the Editor,

The 2023 Antiphospholipid Syndrome (APS) Classification Criteria of the American College of Rheumatology and European League Against Rheumatism include persistently positive lupus anticoagulant (LA), anticardiolipin antibody (aCL) immunoglobulin (Ig)G/IgM, and/or anti-β_2-glycoprotein-I (aβ_2GPI) antibody IgG/IgM [1,2]. However, aCL/aβ_2GPI IgA is not part of the classification criteria due to limited evidence for its thrombogenic potential, its unclear contribution to APS classification [3], and the lack of assay standardization [3,4].

Since the clinical relevance of the IgA isotype is not well determined and it 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 levels (>40 enzyme-linked immunosorbent assay units) of isolated aCL IgA and/or aβ_2GPI IgA positivity.

Among 578 patients evaluated for antiphospholipid antibody (aPL) positivity, we identified only 10 (1.7%) patients with moderate to high levels of isolated aCL IgA or aβ_2GPI IgA positivity (female: 9; white: 4; mean age: 47.5±15.4 years). No patients had histories of thrombosis, pregnancy morbidities, or non-thrombotic complications. Only one patient with isolated aCL IgA had livedo reticularis, and no patients had simultaneous aCL IgA and aβ_2GPI IgA positivity. During the mean prospective follow-up of 7.5±5.9 years following the initial confirmation of aPL positivity, 3/10 (30%) patients experienced the disappearance of aPL.

The prevalence of isolated IgA aCL/aβ_2GPI in patients with or without other systemic autoimmune diseases who present with aPL-related manifestations varies widely between studies due to the different ethnic distributions of the patients and variability in the cut-off levels of IgA. In our cohort of 578 patients evaluated for aPL positivity, only 1.7% of the cases were persistently positive for isolated aPL IgA, supporting previous studies that found the prevalence of isolated aCL/aβ_2GPI IgA positivity to be extremely low.

In 1995, for the first time, Pierangeli et al. [5] demonstrated in vivo that IgA aCL has a role in thrombosis formation. When the pathogenicity of aβ_2GPI IgA was evaluated in a mouse model of thrombosis, the mice inoculated with purified aβ_2GPI IgA had significantly larger thrombi and higher tissue factor expression levels [6]. Although a limited number of small clinical studies, and especially studies of systemic lupus erythematosus, have shown that the 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, arguing against the diagnostic utility of adding aPL IgA to standard testing [7,8,9]. Based on the available data, we agree that routine measurement of IgA does not improve the operative characteristics of aCL and aβ_2GPI IgG/M.

The limitations of our study include the small number of patients (however, isolated IgA positivity is rare) and the lack of a comparison group (thus, we preferred to report our results in a descriptive fashion). Despite these limitations, we believe that a major strength of our study is the inclusion of patients

with persistent moderate-to-high titers of aCL/aβ_2GPI IgA with confirmed negative aCL/aβ_2GPI IgG/M and LA results.

To conclude, based on our small cohort, there is no association between isolated aCL/aβ_2GPI 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.

Keywords: Antiphospholipid syndrome, Antiphospholipid antibody, Immunoglobulin

Anahtar Sözcükler: Antifosfosfolipid sendromu, Antifosfolipid antikoru, İmmünoglobulin

Ethics

Informed Consent: Not required.

Authorship Contributions

Surgical and Medical Practices: A.B.K.D., J.T., D.E.; Concept: A.B.K.D., D.E.; Design: A.B.K.D., D.E.; Data Collection or Processing: A.B.K.D., J.T., D.E.; Analysis or Interpretation: A.B.K.D., D.E.; Literature Search: A.B.K.D., D.E.; Writing: A.B.K.D., D.E.

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