

Four good reasons to appreciate triple positivity

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In the current issue of the *Polish Archives of Internal Medicine (Pol Arch Med Wewn)*, Iwaniec et al¹ showed that the identification of patients with positive results of all 3 tests for the presence of antiphospholipid (aPL) antibodies (lupus anticoagulant [LA], anticardiolipin [aCL], and anti- β_2 -glycoprotein I [anti- β_2 GPI] antibodies, the same isotype [triple positivity]) is not influenced by the method and platform used for their detection.¹ These data provide another piece of evidence on the value of triple positivity in the diagnosis of patients with antiphospholipid syndrome (APS)² and healthy individuals at high risk.³ Thus, triple positivity now displays 4 main features: first, a high association with thromboembolic events; second, no need for confirmation after 12 weeks; third, a strong association with a single pathogenic autoantibody; and fourth, method- and platform-independent detection.

As far as the first feature is concerned, a full positive profile reflects the presence of large amounts of anti- β_2 GPI antibodies with a consequent increased risk of thrombosis-related events.⁴ In this way, it is possible to immediately select a group of individuals at potential risk of cardiovascular events; more complex risk scores taking into account several clinical and biological data may be applied thereafter for a better risk definition and documentation of effectiveness of usual or new treatments.^{5,6}

As for the second feature, current guidelines recommend confirming the initial aPL positivity after 12 weeks to avoid the detection of transient antibodies. In triple-positive individuals, this aPL profile, identified early at the time of the first screening test, is a robust laboratory result that does not need to be confirmed, and the classification of high-risk APS could be anticipated.⁷ This is particularly useful in patients with triple positivity and arterial thrombosis, when the decision on the type of treatment (antiplatelet or anticoagulant drugs) is postponed at the time of confirmation.

Third, triple positivity can be reproduced by spiking normal plasma with immunoglobulin G anti- β_2 GPI affinity purified from plasma of patients positive for all 3 tests.⁸ This indicates that, in individuals with triple positivity, a single autoantibody (anti- β_2 GPI) determines the positivity in all 3 tests used for the diagnosis of APS. A fine specificity to Domain 1 of the β_2 GPI molecule further characterizes this autoantibody and its association with thromboembolic events.^{9,10} Other anti- β_2 GPI antibodies with specificity towards Domain 4/5 of the molecule are not present in triple-positive individuals, and they are not associated with thromboembolic events.¹¹

Finally, the fourth good reason to appreciate triple positivity is that, owing to the large amount of autoantibodies, its identification is easy whichever method is employed. However, the new available chemiluminescent immunoassay using the BIOFLASH technology is far more sensitive and reproducible than the commonly used enzyme-linked immunosorbent assays (ELISAs).¹² Moreover, it is fully automated, thus avoiding the possible pitfalls arising from manual errors of laboratory technicians in performing the ELISA.

In conclusion, triple positivity in aPL assays is comfortable for clinicians because no doubts arise from laboratory and clinical points of view. Physicians still have problems when facing low or borderline positivity of a single aPL test: neither clinical pathologists nor clinicians are happy with this frequent aPL profile as no firm indication for an association with cardiovascular events or their prevention can be derived from such results. In any case, more interaction between clinical pathologists and clinicians is needed in this regard to make sure that the request for aPL screening test is valid and to decide whether aPL test results have clinical significance.

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REFERENCES

- 1 Iwaniec T, Kaczor MP, Celińska-Löwenhoff M, et al. Identification of patients with triple antiphospholipid antibody positivity is platform and method independent. *Pol Arch Med Wewn.* 2016; 126: 19-24.
- 2 Pengo V, Ruffatti A, Legnani C, et al. Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. *J Thromb Haemost.* 2010; 8: 237-242.
- 3 Pengo V, Ruffatti A, Legnani C, et al. Incidence of a first thromboembolic event in asymptomatic carriers of high-risk antiphospholipid antibody profile: a multicenter prospective study. *Blood.* 2011; 118: 4714-4718.
- 4 Pengo V, Biasiolo A, Pegoraro C, et al. Antibody profiles for the diagnosis of antiphospholipid syndrome. *Thromb Haemost.* 2005; 93: 147-152.
- 5 Otomo K, Atsumi T, Amengual O, et al. Efficacy of the antiphospholipid score for the diagnosis of antiphospholipid syndrome and its predictive value for thrombotic events. *Arthritis Rheum.* 2012; 64: 504-512.
- 6 Sciascia S, Bertolaccini ML. Thrombotic risk assessment in APS: the Global APS Score (GAPSS). *Lupus.* 2014; 23: 1286-1287.
- 7 Pengo V, Ruffatti A, Del Ross T, et al. Confirmation of initial antiphospholipid antibody positivity depends on the antiphospholipid antibody profile. *J Thromb Haemost.* 2013; 11: 1-5.
- 8 Pengo V, Biasiolo A, Rampazzo P, Brocco T. dRVVT is more sensitive than KCT or TTI for detecting lupus anticoagulant activity of anti- β 2-glycoprotein-I autoantibodies. *Thromb Haemost.* 1999; 81: 256-258.
- 9 de Laat B, Pengo V, Pabinger I, et al. The association between circulating antibodies against domain I of beta2-glycoprotein I and thrombosis: an international multicenter study. *J Thromb Haemost.* 2009; 7: 1767-1773.
- 10 Pengo V, Ruffatti A, Tonello M, et al. Antiphospholipid syndrome: antibodies to Domain 1 of β 2-glycoprotein 1 correctly classify patients at risk. *J Thromb Haemost.* 2015; 13: 782-787.
- 11 Pengo V, Ruffatti A, Tonello M, et al. Antibodies to Domain 4/5 (Dm4/5) of β 2-glycoprotein 1 (β_2 GP1) in different antiphospholipid (aPL) antibody profiles. *Thromb Res.* 2015; 136: 161-163.
- 12 Bertolaccini ML, Amengual O, Andreoli L, et al. 14th International Congress on Antiphospholipid Antibodies Task Force. Report on antiphospholipid syndrome laboratory diagnostics and trends. *Autoimmun Rev.* 2014; 13: 917-930.