Disappearance of a strong triple positivity for antiphospholipid antibodies after treatment with anakinra

Patients with antiphospholipid syndrome (APS) are mainly managed using antithrombotics to control the hemostasis-activating properties of antiphospholipid antibodies (aPLAbs).

We report the case of a woman with a personal history of late-onset severe pre-eclampsia and late-onset fetal growth restriction during her first pregnancy, when she was 25 years old. Due to fetal distress at 36 weeks of gestation, emergency caesarean section was performed and she delivered a small-for-gestational age male neonate (birth weight: 3rd sex- and gestational-age adjusted percentile). Apgar score at 5 minutes was 6, the boy was admitted into the neonatal intensive care unit for 5 days and left it without any chronic morbidities, the subsequent neuropsychological development being normal.

When the patient was 30 years old, a second and last pregnancy occurred; the secondary prevention of placenta-mediated diseases being assumed by low-dose aspirin, 100 mg daily from 10 weeks of gestation. Gestational hypertension developed from 21 weeks; work cessation and rest were prescribed and labetalol treatment was introduced with good initial efficiency and tolerance. A superimposed term pre-eclampsia acutely occurred at 40 weeks of gestation, leading to caesarean delivery of a normal female neonate, birth weight: 42nd sex- and gestational-age adjusted percentile.

The patient developed an acute left brachiofacial hemiparesis with aphasia when she was 36 years old. Magnetic resonance imaging (MRI) diagnosed stroke in the territory of the left middle cerebral artery. Transoesophageal echocardiography (TOE) revealed moderate aortic insufficiency (AI) associated with a nodular lesion on the aortic valve. A cardioembolic origin was suspected and the patient was treated with fluindione, INR 2.5-3. The control TOE, performed 6 months, later showed that the valvular lesion had completely cleared and treatment was changed for low-dose aspirin, 75 mg daily.

A transient ischemic attack (TIA) occurred in the same cerebral vascular territory when the patient was 40 years old and regularly taking her treatment. Control MRI showed discrete lesions compatible with vascular leucopathy. A spontaneously prolonged activated partial thromboplastin time (aPTT; patient/control ratio: 1.85) was evidenced, but no further specific investigations were performed associated with positive antinuclear antibodies. Control ETO confirmed moderate AI associated with an interauricular septum aneurysm but no patent foramen ovale. Low-dose aspirin was increased to 160 mg daily, associated with atorvastatine, 80 mg daily.

TIA recurred when she was 41. Low-dose aspirin was replaced by clopidogrel, 75 mg daily, and she was finally referred to our outpatient department of haematology for investigations. We evidenced a strong triple positivity for aPLAbs: sustained lupus anticoagulant plasma activity, anticardiolipin IgG (125 GPL units) and anti-β2GP1 IgG (93 units). No underlying systemic disease could be diagnosed after extensive investigations, leading to the diagnosis of primary antiphospholipid antibody (aPLAb) syndrome (APS). Warfarin was introduced, target INR 2.5-3. The patient was subsequently regularly followed up every 6 months by a multidisciplinary team (neurologist, cardiologist, nephrologist, internist, and haematologist) in our outpatient department. The persistently positive triple positivity for aPLAbs was systematically confirmed each semester, with no significant variations in aPLAb titres, over a 7 year time frame (15 blood samples, all showing similar results). No clinical or biological significant evolution occurred until she was 48 (Figure 1).

A systematic control echocardiography evidenced an asymptomatic pericardial effusion, 400-500 ml: colchicine was introduced, 1 mg per day, with a significant decrease of the effusion volume one month later, regular follow up showing stabilization. The triple positivity for aPLAbs was once more confirmed. After nearly one year, severe asthenia impacting on work capacities developed and a significant compression of the right atri-

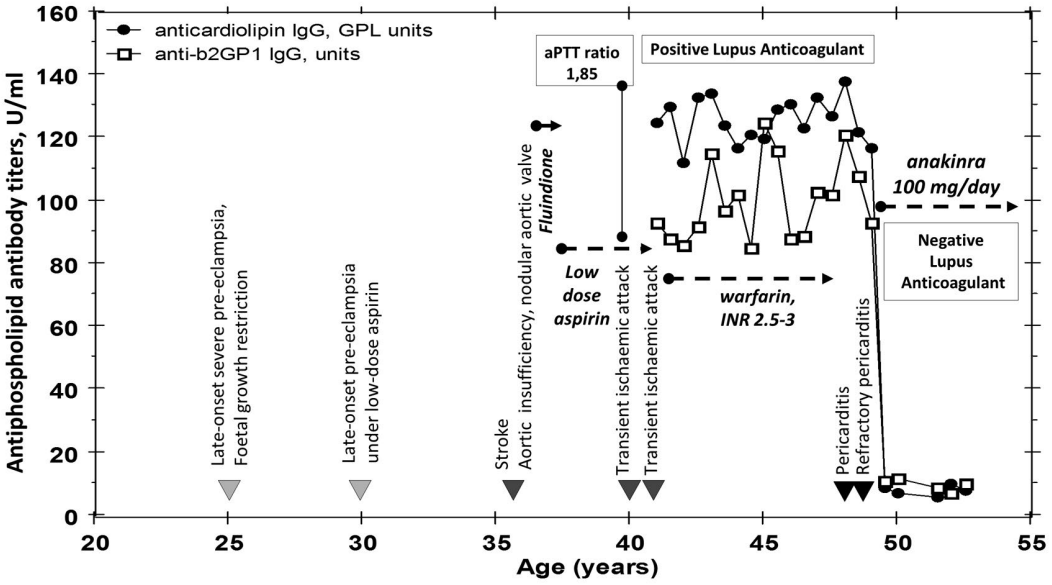

Figure 1. Key clinical and laboratory findings obtained during the follow up of the patient.

um by progression of the pericardial effusion was evidenced. A pericardial puncture removed 700 ml of citric fluid, which microbiological, cytological, biochemical and serological analysis concluded was due to an exsudative effusion (August 2016). One month later, the patient was readmitted for acute inflammatory pericarditis (C-reactive protein: 120-180 mg/L): colchicine was stopped, and warfarin was stopped and replaced by weight-adjusted low molecular weight heparin to allow ibuprofen treatment, 1.8 g per day for 4 weeks, together with 400 mg hydroxochloroquine per day. The initial effect on the symptomatology was favourable.

This new clinical feature led us to question the onset of an underlying systemic disease, and consequently a secondary APS. First, a systemic lupus erythematosus. Among the 11 criteria defined by the American College of Rheumatology ACR in 1982[1] and updated in 1997,[2] pericarditis was the only clinical criteria, positive antinuclear antibodies ANA (1:640) and positive aPLAbs the only 2 biological criteria, thus not reaching the threshold of 4 positive criteria. We also did not fulfil at least 4 (only 3) of the 17 criteria edited by the Systemic Lupus International Collaborating Clinic (SLICC) group.[3] There was nothing pointing to another systemic inflammatory disease. Clinical examination, complete blood cell count and positron emission tomography with ^{18}F-fluorodeoxygluco (FDG-PET scan) allowed us to rule out cancer, as much as feasibly possible. Testing for an infectious disease was negative. The patient was not taking any drug prone to induce secondary APS.

Recurrence of acute inflammatory pericarditis occurred one month later with moderate compression of the right cardiac cavities on echocardiography which caused us to stop ibuprofen and introduce prednisolone, 1 mg per kg per day. Long-term persistence of the strong triple positivity for aPLAbs was confirmed. A second recurrence occurred 3 months later and led us to progressively decrease steroids, stop hydroxochloroquine and introduce subcutaneous anakinra, 100 mg per day; there was a quick improvement of the clinical symptomatology and of the inflammatory markers which were all within normal range after 2 weeks. Pericarditis remission was confirmed on the regular follow-up medical visits; echocardiography showing no more pericardial effusion.

New global evaluations were performed as the patient was asymptomatic and treated by anakinra for 3 then 6 months. Clinical exams were normal. Complete blood cell count values were within normal range with negative direct Coombs tests, as was complement including its C3 and C4 fractions, anti-dsDNA antibodies and renal function. Antinuclear antibodies were positive (1:640) but anti-Sm antibodies were negative, as were anti-ENA antibodies. The aPLAbs antibodies had become negative. This negativity of aPLAbs was persistent and confirmed on the four subsequent screenings performed during each trimestral follow-up visit.

The spontaneous disappearance of a persistent strong triple positivity for aPLAbs is very unlikely to occur.[4] The direct pathophysiological link with the treatment with recombinant human IL-1 receptor antagonist (IL-1Ra), anakinra, remains to be elucidated. IL-1Ra-deficient mice develop autoimmunity and arthritis spontaneously due to excess IL-1 signalling causing autoimmunity, endogenous IL-1β being involved in T-cell dependent antibody production.[5] Treatment of rheumatoid arthritis with anakinra induces an increase of regulatory T cells,[6] which can suppress B-cell responses and autoantibodies.[7] Our hypothesis is that treatment with IL-1 receptor antagonists may be prone to controlling anti-β2GP1 autoantibodies and the associated aPLAbs. This warrants further investigations and controlled prospective multicenter studies. In patients with APS, an immunomodulatory approach may be complementary to antithrombotics. This is reinforced by the recent report of the disappearance of aPLAbs in 2 patients with systemic lupus erythematosus and APS while on belimumab, a monoclonal antibody that blocks the binding of circulating B-cell activating factor to its target receptors on B cells.[8]

More generally, this case report on anakinra, together with the recent one on belimumab,[8] underlines the need for a systematic review focusing on the effects of immunomodulating therapies on the fluctuation of aPL Abs. However, regarding the effect of rituximab on aPLAb profiles, a review of 90 aPLAb-positive patients described in 50 articles, cited by the Antiphospholipid Antibody Task Force,[9] concluded that no case report has yet described a patient with a clinically significant persistently positive aPL Ab profile who became negative for aPLAb following treatment with only rituximab. We must therefore ascertain whether any of these treatments has a general effect, varying from one patient to another, or whether what we report is merely a result of out of the norm reactivity. We deem this necessary before designing a specific randomized controlled trial, with the difficulties it entails.

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doi:10.3324/haematol.2018.205484

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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