Autoimmune type antiphospholipid antibodies in a patient with q fever

Q fever is a zoonosis caused by Coxiella burnetti which has been associated with a range of haematological manifestations like bone marrow necrosis, haemophagocytosis, haemolytic anaemia, transient monoclonal gammopathy, lymphadenopathy mimicking lymphoma, transient hypoplastic anaemia and spontaneous splenic rupture. Also a number of autoantibodies have been reported in association with acute Q fever including antiphospholipid antibodies –aPA- (lupus anticoagulant-LA-, anticardiolipin -aCA- and anti-β2 glycoprotein-I-β2gpI-) which are one of the most relevant autoimmune markers reported in this setting.[1]

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Typically (but not always) the aPA transiently found in association to infectious diseases belong to the *infectious type* (β2gpI-independent) as opposed to the *autoimmune type* (β2gpI-dependent) frequently reported in patients with autoimmune disorders. This positivity for anti-β2gpI antibodies along with LA are considered the most specific aPA for the development of clinical manifestations of the antiphospholipid syndrome, but still an increased thrombotic risk has been reported for individuals with the so called *infectious-type aPA*.[2,3]

We report a case of a patient with acute Q fever who developed a transient strong global positivity for LA, aCA and anti-β2gpI consistent with autoimmune type aPA.

A 39-year-old woman presented with isolated spiking fever, fatigue, myalgias and arthralgias over the last 2 weeks and hepatosplenomegaly as the sole relevant abnormality on examination. Serum biochemistry revealed an isolated abnormality of liver function tests with normal bilirrubin levels. A positive serological result for phase II indirect immunofluorescence for Coxiella burnetti (IgM 1/256) confirmed the diagnosis of acute Q fever; other microbiological test results were irrelevant for diagnostic purposes. A prolonged APTT which did not correct in mixing studies and showing diagnostic criteria for LA was found;[4] as well as high titre aCA (both IgG and IgM) and anti-β2gpI antibodies were found (the results of diagnostic tests for aPA have been summarized in Table 1).

Table 1. Summary of the results of the aPA-related tests during admission as well as during the follow-up.

	May 2004	*July 2004*	*September 2004*
APTT/APTT ratio	70.6"/2.1"	52.8"/1.6	35.3"/1.08
PT/PT ratio	15.6"/1.2	13.7"/1.1	12.6"/1.03
1:1 mix (immediate)	57.6"	38.2"	-------
1:1 mix (1h incubation)	65.2"	37.1"	-------
PTT-LA ratio*	2.5	1.6	1.1
dRVVT*ratio	1.9	1.1	1.01
Staclot LA*	Positive	Positive	Negative
aCA (IgG) (GPL/mL)	>300	21	15
aCA (IgM) (MPL/mL)	>300	4.6	5.1
Anti-β2-gpI (U/mL)	59	0.9	1.3
Platelet count (x10^9/L)	144	257	360

Normal ranges: APTT (normal 27"-35") PT (normal 14.1-20.5")
PTT-LA ratio≤1.2 dRVVT ratio <1.2 aCA (IgG/IgM) /Anti-β2-gpI 0-15
APTT: Activated partial thromboplastin time PT: Prothrombin time
dRVVT: dilute Russell viper venom time Staclot-LA: Phospholipid neutralization assay

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Other autoimmune markers were tested and their results can be seen in Table 2. The patient became asymptomatic (and her temperature became gradually normal) over the next 3 weeks after discharge and positivity for aPA was lost during a 4-month follow-up period. Hepatosplenomegaly persisted for 8 weeks after hospital discharge.

Table 2. Results of other autoimmune markers at the time of admission.

ANA Negative	RF 54 UI/mL (normal: 0-14)
AMA Negative	Cryoglobulins Negative
ASMA +1/160	C3c 127.7 (normal 90-180)
APCA Negative	C4 25.8 mg/dL (normal 10-40)
ALKM Negative	PCR-HS 194.7 (normal 0-5)

Antiphospholipid antibodies have been reported to be a common event in the setting of infection by Coxiella burnetti; actually the prevalence of aCA and LA is between 42-84% and 76% respectively.[5,6] IgM isotypes of aCA are mainly produced but IgG elevations are also often found. To our knowledge there are no data available on the prevalence of anti-β2-gpI antibodies in patients infected by this microorganism. Some authors have suggested that given this consistent association between a prolongation of the APTT over 10 seconds the control time and a clinical scenario consistent with Q fever can be useful to reinforce the degree of suspicion of Q fever, especially in cases like ours in which fever is the only presenting feature and an aPA can be demonstrated.[7] Anyway these clinical and biological features can be reproduced in a number of other infectious diseases and lack any reasonable degree of specificity to give them such a degree of diagnostic value.

Antiphospholipid antibodies complicating acute Q fever are transient in virtually all cases and they tend to clear before the positivity of specific serological assays does (IgM can persist beyond 6 months in over 3 out of every 4 patients).[5] From the experience coming from transient LA found in children often in association to infection clearance of the antibody often follows a stepwise pattern similar to the one in our patient with correction of APTT in mixing studies (as an expression of weakening of LA) and of dRVVT being the first screening tests to become negative.[8]

There has been a good deal of debate with regard to the pathogenetic mechanism involved in the development of aPA of infectious origin. Recent research has provided some evidence that molecular mimicry (this is strong homology) between certain peptides belonging to the pathogens and behaving as target epitopes for anti-β2-gpI antibodies and β2-gpI might be the key factor for the induction of aPA.[6,9] This is the case for the peptides LKTPRV and KDKATF of Coxiella burnetti which are shared by many other viral, bacterial or parasitic microorganisms.[10] It is believed that pathogen particles are digested and presented on macrophages, dendritic cells or B cells; these pathogen particles are presented to T cells, which along with appropriate HLA presentation and Th1/Th2-activated cytokine cascade expression, will lead to generation of plasma cells secreting anti-β2-gpI antibodies, directed to the pathogen particles, which share structural homology (molecular mimicry) with the β2-gpI molecule.[6] Whether individuals will develop antiphospholipid syndrome will depend mainly on their genetic background.

Therefore aPA in patients with Q fever is a real autoim-

mune phenomenon; phase II antibodies to Coxiella burnetti and aCA are different antibodies and the aCA activity in patients with Q fever is β2-gpI-independent in over 85% of cases. Occasionally Q fever-associated aPA are of the autoimmune type but no manifestation of the antiphospholipid syndrome has been reported in those cases so far.[5] Our patient is an example of this type of aPA presenting with a strong and asymptomatic positivity for all the aPA routinely tested.

The general lack of thrombotic complications associated to these type of aPA makes any type antithrombotic therapy unnecessary; however the slightly increased risk of thrombosis reported in individuals with infectious-driven aPA[2,3] makes prophylactic measures reasonable during the positivity of the antibodies should clinical situations susceptible of a significantly increased thrombotic risk arise during that period.

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