

EXTENDED REPORT

Antiphospholipid syndrome associated with infections: clinical and microbiological characteristics of 100 patients

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Objective: To describe and analyse the clinical characteristics of 100 patients with antiphospholipid syndrome (APS) associated with infections.

Methods: Patients were identified by a computer assisted search (Medline) of published reports to locate all cases of APS published in English, Spanish, and French from 1983 to 2003. The bilateral Fisher exact test was used for statistics.

Results: 59 female and 41 male patients were identified (mean (SD) age, 32 (18) years (range 1 to 78)): 68 had primary APS, 27 had systemic lupus erythematosus, two had "lupus-like" syndrome, two had inflammatory bowel disease, and one had rheumatoid arthritis. APS presented as a catastrophic syndrome in 40% of cases. The main clinical manifestations of APS included: pulmonary involvement (39%), skin involvement (36%), and renal involvement (35%; nine with renal thrombotic microangiopathy, RTMA). The main associated infections and agents included skin infection (18%), HIV (17%), pneumonia (14%), hepatitis C (13%), and urinary tract infection (10%). Anticoagulation was used in 74%, steroids in 53%, intravenous immunoglobulins in 20%, cyclophosphamide in 12%, plasma exchange in 12%, and dialysis in 9.6%. Twenty three patients died following infections and thrombotic episodes (16 with catastrophic APS). Patients given steroids had a better prognosis ($p=0.024$). The presence of RTMA and requirement for dialysis carried a worse prognosis ($p=0.001$ and $p=0.035$, respectively).

Conclusions: Various different infections can be associated with thrombotic events in patients with APS, including the potentially lethal subset termed catastrophic APS. Aggressive treatment with anticoagulation, steroids, and appropriate antibiotic cover is necessary to improve the prognosis.

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The detection of antiphospholipid antibodies (aPL)—that is, lupus anticoagulant or anticardiolipin antibodies—is of interest because of their importance in the pathogenesis of clotting in the antiphospholipid syndrome (APS). APS occurs not only in systemic autoimmune diseases, particularly systemic lupus erythematosus (SLE), but also in patients who do not manifest overt symptoms of other autoimmune disturbances (primary APS), where the emphasis is primarily on vascular events.^{1 2}

Since 1983, many infections have been found to be associated with aPL positivity, although a pathogenic role for these antibodies was not usually obvious except in a few isolated cases. Over recent years it has been emphasised and reported on several occasions^{3–5} that many infections may not only trigger the production of these antibodies but also appear to be accompanied by clinical manifestations of the APS itself. This has been seen particularly in patients with catastrophic APS.^{6–8}

In this study we made the first literature analysis—some 20 years after the definition of APS—of patients who developed an APS associated with, and probably triggered by, infections. In this series, comprising a total of 100 patients, we further clarify the importance of this association and discuss other clinical aspects, including treatment and prognosis.

METHODS

Patients were identified by a computer assisted search of published reports (Medline, National Library of Medicine, Bethesda, Maryland, USA) to locate all cases of APS published in English, Spanish, and French from 1983 (when APS was first defined) to 2003.

We also analysed several original cases that were categorised as having APS or as having aPL or lupus anticoagulant associated with any infection in which there was a thrombotic process. We scanned bibliographies of all articles for references not identified in the initial search. Only cases with well documented clinical summaries and relevant information were included in the review.

Data from these papers were summarised using a standardised data form, including sex, age, diagnosis of the underlying condition, associated infections, major thrombotic clinical manifestations, immunological features, treatment, and course. Two new cases of APS from our clinics, both associated with urinary infection, are added to the review as illustrative case reports (see the appendix).

The bilateral Fisher exact test was used for statistics.

RESULTS

In all, 100 patients with APS manifestations associated with infections were reviewed: 98 from the literature search^{6–56} plus two from our own clinics.

General characteristics

General clinical features of these patients are shown in table 1. Fifty nine per cent were female and 41% male. Their mean (SD) age was 32 (18) years (range 1 to 78). There were 24 young patients (under 18 years), who were affected mainly by skin and respiratory infections. Sixty eight patients had primary APS, 27 had SLE, two had "lupus-like" disease, two had inflammatory bowel disease (one Crohn's disease

Abbreviations: aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; RTMA, renal thrombotic microangiopathy

Table 1 General characteristics

	Per cent (n = 100)
Female	59
Male	41
SLE	27
Primary APS	68
Catastrophic APS	40
Lupus-like	2
Rheumatoid arthritis	1
IBS	2

APS, antiphospholipid syndrome; IBS, inflammatory bowel disease.

and one ulcerative colitis), and one had rheumatoid arthritis. In 40 of the 100 cases, the thrombotic events appeared in the form of catastrophic APS.

Clinical presentation

Pulmonary involvement was present in 39 patients: in 24 as adult respiratory distress syndrome (ARDS), in 18 as pulmonary embolism, in three as pulmonary haemorrhage, and in one as pulmonary hypertension. Skin involvement was reported in 36 patients: 16 had livedo reticularis, nine had purpura fulminans, eight had skin ulcers, and three had digital necrosis. Renal involvement was reported in 35 patients, nine of whom had renal thrombotic microangiopathy (RTMA). Almost one third of the patients (31%) had cerebral disease, manifested as cerebrovascular accidents (CVA) in 21 patients, encephalopathy in seven, and other cerebral features in seven, including seizures, psychosis, or cerebral microinfarcts. Peripheral thrombosis was reported in 30 patients (15 had deep vein thrombosis). Other types of vascular thrombosis were: femoral artery occlusions in nine patients, vena cava thrombosis in four, radial artery thrombosis in one, and thrombosis of other arteries in three. Cardiac disease was found in 24 patients, presenting as myocardial infarction in 12, valve lesions in 10, and cardiac microthrombi in one; other cardiac features were reported in five (cardiogenic shock and atrial thrombus). Ten patients had avascular necrosis of the hip joint, in all cases accompanied by HIV infection. In only one case was the previous use of steroids reported (given for thrombocytopenia). We excluded all cases with other possible causes of avascular necrosis, including high triglyceride levels or protease inhibitor use. The remaining APS manifestation are summarised in table 2.

Associated infections

The associated infections and microbiological agents are shown in table 3. Skin infection (18%), human immunodeficiency virus (HIV) infection (17%), pneumonia (14%), hepatitis C virus (HCV) infection (13%), and urinary infection (10%) were the commonest associated infections. In nine cases, more than one organ or agent was identified as a source of infection. Other infections less frequently associated with APS were identified, including mycoplasma (3), cytomegalovirus (CMV) (3), fungal infections (2), pulmonary tuberculosis (2), malaria (2), *P carinii* (1), and leptospirosis (1).

Treatment

Most of the patients received the appropriate antibiotic and antiviral treatment according to the underlying infection. In five cases, this was given as sole treatment. The treatment was not reported in 17 cases. Table 4 shows the differing types of treatment used. Anticoagulation was the most common, used in 61 of 83 patients (73%). Steroids were

used in 43 patients (53%), intravenous immunoglobulins in 17 (20%), cyclophosphamide in 10 (12%), and plasma exchange in 10 (12%). Aspirin was used in six patients (7%), dialysis in eight (10%), fibrinolytics in six (7%), and fresh frozen plasma in five (6%). Different types of surgical procedures were undertaken, including arthroplasty in three (4%), leg amputation in two (2%), and vena cava filter, aortic repair, or splenectomy in one case (1%) each.

Outcome

Twenty three patients died following infection and thrombotic episodes (in 16 cases with catastrophic APS). Other causes of death were related to RTMA (four cases), purpura fulminans (one case), CVA in a patient with varicella pneumonia, and HIV infection in one patient. Patients who received steroids had a better prognosis than the rest ($p = 0.024$). The presence of RTMA and need for dialysis carried a worse prognosis ($p = 0.001$ and $p = 0.035$, respectively). The remaining 77 patients recovered after the thrombotic event.

Table 2 Manifestations of antiphospholipid syndrome

	Per cent (n = 100)
<i>Pulmonary</i>	39
ARDS	24
Pulmonary embolism	18
Pulmonary haemorrhage	3
Pulmonary hypertension	1
<i>Skin</i>	36
Livedo reticularis	16
Purpura fulminans	9
Skin ulcers	8
Digital necrosis	3
<i>Renal</i>	35
RTMA	9
<i>Cerebral</i>	31
CVA	21
Encephalopathy	7
Other cerebral	7
<i>Peripheral thrombosis</i>	30
DVT	15
Femoral artery	9
Caval thrombosis	4
Radial artery	1
Other arteries	3
<i>Cardiac</i>	24
Myocardial infarction	12
Valve lesion	10
Cardiac microthrombi	1
Other cardiac	5
<i>Intra-abdominal</i>	
Hepatic	12
Splenic	8
Neuropathy	7
Intestinal	6
Mesenteric	5
Portal	4
Pancreas	3
<i>Others</i>	
Avascular necrosis	10
Genital	2
Amaurosis fugax	2
Other manifestations	6

ARDS, adult respiratory distress syndrome; CVA, cerebrovascular accident; DVT, deep vein thrombosis; RTMA, renal thrombotic microangiopathy.

Table 3 Associated infections

Agent or type	Per cent (n = 100)*
Skin	18
HIV	17
VZV	15
Pneumonia	14
HCV	13
Urinary	10
Upper respiratory	9
Sepsis	6
Gastrointestinal	6
Staphylococci	4
Streptococci	4
<i>E coli</i>	4
Other Gram negative	3
Mycoplasmas	3
CMV	3
Malaria	2
Fungal	2
Tuberculosis	2
<i>P carinii</i>	1
Amoebiasis	1
Other viruses	3
Other infections	6

*Note: in some patients more of one infection occurred.
 CMV, cytomegalovirus; HIV, human immunodeficiency virus;
 HCV, hepatitis C virus; VZV, varicella-zoster virus.

DISCUSSION

aPL were originally detected in human serum by Wasserman⁵⁷ almost 100 years ago, when his complement fixation test was first used for the diagnosis of syphilis, and when the Venereal Disease Research Laboratory (VDRL) test was described.⁵⁸ A phospholipid termed cardiolipin was the major tissue extract used in this test. It was subsequently found that the VDRL was not specific for syphilis but was also positive in autoimmune diseases such as SLE. In 1983, cardiolipin was used for the first time as the antigen in a solid phase aPL specific assay by Harris *et al*,⁵⁹ and the term APS was born.⁶⁰ Syphilis was thus the first infection to be recognised as being linked to aPL. Since 1983, many other infections have been found to be associated with the presence of aPL, although a pathogenic role for these antibodies was not usually obvious except in a few isolated cases.

In 1990, it was found that the binding of the aPL to phospholipid was enhanced in autoimmune conditions by a "cofactor" known as β_2 glycoprotein I (β_2 GPI)—a glycoprotein with anticoagulant properties—whereas the "non"-thrombogenic aPL did not require this cofactor to enhance binding. The two types of aPL were referred to as "autoimmune" and "infectious" types.⁶¹⁻⁶⁴ This distinction, however, was subsequently found not to be absolute,⁶⁵⁻⁶⁸ and it was postulated that infections may be a trigger factor for

the induction of pathogenic aPL in certain predisposed individuals. In the present study, we have analysed the clinical and microbiological characteristics of 100 patients in whom pathogenic or thrombogenic aPL appeared in the course of an infectious process.

Microbial agents or viruses may induce autoimmune disease by several mechanisms. Although the specific factors resulting in the induction of aPL and the associated thrombotic events are still unknown, "molecular mimicry" and various infectious agents acting as superantigens have been proposed as mechanisms. Antigenic similarity between infectious agents and host tissues might result in an immune response to the shared determinant, resulting in disease. Polyclonal activation by the proteins of some infectious agents may act on particular subsets of the lymphocyte population—for example, viruses may destroy a particular T cell subset, upregulate Th1 cytokines, selectively activate other T cell subsets, and directly stimulate cytokine and chemokine release, which may influence the expression of MHC class I and class II molecules.⁶⁹⁻⁷¹ A hexapeptide (TLRVYK) has been identified by Blank *et al*.⁷² This is specifically recognised by a pathogenic anti- β_2 GPI monoclonal antibody. An evaluation of the pathogenic potential of a variety of microbial pathogens carrying sequences related to this hexapeptide in mice was carried out by the same group by infusing IgG specific to the peptide intravenously into naive mice. High titres of anti-peptide anti- β_2 GPI antibodies were observed in mice immunised with *H influenzae*, *N gonorrhoea*, and tetanus toxoid. Significant thrombocytopenia, prolonged activated partial thromboplastin times, and increased percentages of fetal loss were also observed.⁷² Zhang *et al* recently identified an *S aureus* protein (Sbi) which also bound β_2 GPI and could serve as a target molecule for IgG binding.⁷³ Gharavi *et al* showed that synthetic peptides which share both structural similarity with the putative phospholipid binding region of the β_2 GPI molecule and a high homology with CMV were able to induce aPL in NIH/Swiss mice.⁷⁴⁻⁷⁵

Many viral infections may be accompanied by increases in aPL.⁷⁶⁻⁸⁸ Among these, HCV⁷⁶⁻⁸¹ and HIV⁸⁵⁻⁸⁸ infections have been intensively studied. In 1986, Bloom *et al* first documented lupus anticoagulant in 44% of AIDS patients and in 43% of asymptomatic HIV positive individuals (in which they may be transient).⁸⁵ The anticardiolipin antibodies described in HIV patients are of both the pathogenic (β_2 GPI cofactor dependent) and the infectious type (β_2 GPI independent).⁸⁶⁻⁸⁸ As HIV infection leads to immunosuppression affecting mainly CD4+ cells and macrophages, it is possible that the pathophysiological mechanism of APS associated with HIV is different from that in other infections.

Many bacterial infections are associated with aPL. However, the increase is not usually associated with thrombotic events. Of interest, however, is the fact that—although β_2 GPI dependence is usually not present in this group—in patients with leprosy (particularly in the multi-bacillary type of leprosy) the anticardiolipin antibodies may be β_2 GPI dependent, as is found in autoimmune diseases.⁸⁹ Lucio's phenomenon is a rare manifestation of leprosy in which the histopathological findings are related to microvascular thromboses in the absence of inflammatory infiltration of the vessel walls. Levy *et al* showed that this type of leprosy was associated with β_2 GPI dependency of the anticardiolipin antibodies.⁹⁰ One patient has been documented—a young adult who developed an APS in childhood following a pulmonary infection with *M pneumoniae*.⁹¹ Streptococcal infections may also be associated with raised titres of anticardiolipin antibodies. There has been controversy over rheumatic heart disease, with some investigators reporting raised titres and others not confirming these findings.

Table 4 Treatment given in 83 cases*

	n	%
Anticoagulation	61	74
Steroids	44	53
Immunoglobulins	17	20
Cyclophosphamide	10	12
Plasma exchange	10	12
Dialysis	8	10
Aspirin	6	7
Fibrinolytics	6	7
Fresh frozen plasma	5	6
Arthroplasty	3	4
Cyclosporin	2	2
Splenectomy	1	1
Other treatments	7	8

*Treatment not specified in 17 cases.

Q fever, caused by *Coxiella burnetii*, is also associated with a high frequency of anticardiolipin antibody positivity.

Of particular interest is the unusual but potentially fatal subset of catastrophic APS.⁹² Until now, more than 200 such patients have been collected in an international registry.^{52, 93–95} Forty patients from the present series (40%) developed catastrophic APS after infectious episodes. Several triggering factors became apparent when these cases were analysed. These included trauma, withdrawal of anticoagulation, and carcinoma, but particularly infections.⁹³ The latest published analysis⁶ has shown that no less than 24% of catastrophic APS cases were preceded by infections. These comprised respiratory (10%), cutaneous, including infected leg ulcers (4%), urinary tract (4%), gastrointestinal (2%), general sepsis (1%), and other infections (3%). Molecular mimicry has also recently been proposed for the development of catastrophic APS following infections.⁹⁶

Regarding treatment, in the present study we found that a wide variety of treatments had been given. Most patients received anticoagulants (74%) plus immunosuppressive or immunomodulatory treatment. Patients who received steroids had a better prognosis than those who did not. Recently, Annane *et al* showed that the use of steroids reduced the risk of death in patients with septic shock and relative adrenal insufficiency.⁹⁷ Furthermore, guidelines for the treatment of patients with catastrophic APS have recently been published⁹⁵ and include the prompt use of antibiotic cover if infection is suspected.

Conclusions

A wide variety of infections can be associated with thrombotic events in patients with APS, including the potentially lethal subset termed catastrophic APS. A disproportionately large number of patients develop catastrophic APS following infection, bearing in mind the small number of catastrophic cases documented in published reports (around 200) as opposed to the several thousand with simple/classic APS. This emphasises a major difference in the pathogenesis between the two conditions that remains to be explored in future studies, and also the need for early diagnosis and aggressive antibiotic treatment as soon as infection is suspected in a patient with APS.

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APPENDIX

CASE 1

A 42 year old white women was diagnosed with SLE 25 years ago. Over the following years she had several exacerbations of articular involvement, with progressive hand deformity (Jaccoud arthropathy) and oral ulcers that resolved with small doses of corticosteroids and non-steroidal anti-inflammatory drugs. In 1992, Libman-Sacks endocarditis and livedo reticularis were detected and laboratory tests showed the presence of lupus anticoagulant. She began treatment with acenocumarol. Six months later, she was admitted because of a urinary tract infection. Urine cultures were positive for *E coli*. She was treated with ciprofloxacin and discharged in good condition. The day after discharge, she developed epigastric pain accompanied by nausea, vomiting, diarrhoea, and fever (39°C). She had livedo reticularis and lower limb oedema and complained of upper abdominal pain (with

normal peristalsis) and occasional chest discomfort. A systolic murmur was detected in the mitral valve area.

Laboratory tests revealed a marked rise in transaminases (aspartate transaminase 1313 I/U, alanine transaminase 1530 I/U), alkaline phosphatase (353 I/U), and lactic dehydrogenase (3735 I/U). The platelet count was $88 \times 10^9/l$, haemoglobin 8.8 g/l, packed cell volume 26%, white blood count (WBC) $7 \times 10^9/l$, and creatinine 1.9 mg/dl. Direct and indirect Coombs tests were positive. Peripheral blood smears showed no evidence of schistocytes. The erythrocyte sedimentation rate (ESR) was 93 mm/h, anti-ds-DNA was positive; complement levels were low (C3 = 0.117, C4 < 0.07, and CH50 activity = 7); 24 hour urinary protein excretion was 538 mg. IgG anticardiolipin antibodies and lupus anticoagulant were positive, with negative IgM anticardiolipin antibodies. An ECG revealed ST segment and T wave abnormalities. Echocardiography showed mitral insufficiency and a valvar vegetation. Left ventricular size and function appeared normal. There was an inferior hypokinesia. There was enzymatic evidence of a myocardial infarct (creatinine phosphokinase MB isoenzyme, 151 I/U; troponin I, 132 I/U). Coronary angiography showed 100% occlusion of the proximal right coronary artery.

A stent was inserted with good results. She started treatment with clopidogrel, aspirin, heparin, and β blockers. She was also treated with intravenous "pulse" methylprednisolone for the haemolytic anaemia, without improvement. Her platelet count fell to $35 \times 10^9/l$. Intravenous immunoglobulin treatment was started. Her clinical course then stabilised and a gradual improvement occurred. She was diagnosed as having catastrophic APS with renal, cardiac, and hepatic involvement associated with a urinary infection by *E Coli*.

CASE 2

The patient was a 78 year old women with an eight year history of seizures treated with oral carbamazepine. She presented with chest pain and generalised soft tissue oedema of her lower right limb. Physical examination was unremarkable except for leg pain and oedema. Laboratory investigations showed an ESR of 14 mm/h, packed cell volume 39%, haemoglobin 12.7 g/l, WBC $7480 \times 10^9/l$, platelet count $155 \times 10^9/l$, creatinine 0.8 mg/dl, anti ds-DNA negative, and antinuclear antibodies (ANA) 1/40. Urinalysis showed the presence of white cells and culture for *E coli* was positive. Ciprofloxacin treatment was given. External iliac vein and femoral thrombosis was diagnosed by the Doppler technique. Pulmonary scintigraphy showed a perfusion mismatch with a high probability of pulmonary embolism. She was diagnosed as having deep vein thromboses and pulmonary embolism. The thrombophilia tests showed positive lupus anticoagulant with negative anticardiolipin antibodies.

She began anticoagulation with heparin and acenocumarol. During the admission, she suddenly developed epileptic seizures. Computed tomography of the brain revealed lacunar infarcts. A diagnosis of primary APS associated with a urinary infection by *E coli* was made.

REFERENCES

- 1 Asherson RA. A "primary" antiphospholipid syndrome. *J Rheumatol* 1988;15:1742–4.
- 2 Asherson RA, Khamashta MA, Ordi-Ros J, *et al*. The "primary" antiphospholipid syndrome: major clinical and serological features. *Medicine (Baltimore)* 1989;68:366–76.
- 3 Shoenfeld Y, Blank M, Krause I. The relationship of antiphospholipid antibodies to infections – do they bind to infecting agents or may they even be induced by them? *Clin Exp Rheumatol* 2000;18:431–2.
- 4 Uthman IW, Gharavi AE. Viral infections and antiphospholipid antibodies. *Semin Arthritis Rheum* 2002;31:256–63.
- 5 Dalekos GN, Zachou K, Lioskos C. The antiphospholipid syndrome and infection. *Curr Rheumatol Rep* 2001;3:277–85.

- 6 Asherson RA, Cervera R, Piette JC, Shoenfeld Y, Espinosa G, Petri MA, et al. Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. *Medicine (Baltimore)* 2001;**80**:355-77.
- 7 Hayem G, Kassis N, Nicaise P, Bouvet P, Andrement A, Labarre C, et al. Systemic lupus erythematosus associated with catastrophic antiphospholipid syndrome occurring after typhoid fever. A possible role of Salmonella lipopolysaccharide in the occurrence of diffuse vasculopathy-coagulopathy. *Arthritis Rheum* 1999;**42**:1056-61.
- 8 Grinberg AR, Heller PG, Correa G, Sarano JF, Molinas FC, Nicasato MA, et al. Síndrome antifosfolípido catastrófico: comunicación de dos formas de presentación. *Medicina (Buenos Aires)* 1999;**59**:743-6.
- 9 Rojas-Rodríguez J, García-Carrasco M, Ramos-Casals M, Enriquez-Coronel G, Colchero C, Cervera R, et al. Catastrophic antiphospholipid syndrome: clinical description and triggering factors in 8 patients. *J Rheumatol* 2000;**27**:238-40.
- 10 Scully RE, Mark EJ, McNelly W, McNelly BU. Case records of the Massachusetts General Hospital. *N Engl J Med* 1990;**322**:754-69.
- 11 Abinader A, Hanly AJ, Lozada CJ. Catastrophic antiphospholipid syndrome associated with anti-beta-2-glycoprotein I IgA. *Rheumatology* 1999;**38**:84-5.
- 12 Maddison PJ, Thorpe C, Seale JRC, Ahmed W, Whiteley GS. Grand rounds from international lupus centres: "catastrophic" antiphospholipid syndrome. *Lupus* 2000;**9**:484-8.
- 13 Amital H, Levy Y, Davidson C, Lundberg I, Harju A, Kosach Y, et al. Catastrophic antiphospholipid syndrome: remission following leg amputation in 2 cases. *Semin Arthritis Rheum* 2001;**31**:127-32.
- 14 Undas A, Swadzba J, Undas R, Musial J. Three episodes of acute multiorgan failure in a woman with secondary antiphospholipid syndrome. *Pol Arch Med Wewn* 1998;**100**:556-60.
- 15 Jou IM, Liu MF, Chao SC. Widespread cutaneous necrosis associated with antiphospholipid syndrome. *Clin Rheumatol* 1996;**15**:394-8.
- 16 Cisternas M, Gutierrez MA, Rosenberg H, Jara A, Jacobelli S. Catastrophic antiphospholipid syndrome associated with crescentic glomerulonephritis: a clinicopathologic case. *Clin Exp Rheumatol* 2000;**18**:252-4.
- 17 Scully RE, Mark EJ, McNeely WF, Ebeling SH, Ellender SM. Case records of the Massachusetts General Hospital. *N Engl J Med* 1999;**340**:1900-8.
- 18 Falcini F, Taccetti G, Ermini M, Trapani S, Cerinic MM. Catastrophic antiphospholipid antibody syndrome in pediatric systemic lupus erythematosus. *J Rheumatol* 1997;**24**:389-92.
- 19 Greisman SG, Thayaparan RS, Godwin TA, Lockshin MD. Occlusive vasculopathy in systemic lupus erythematosus. Association with anticardiolipin antibody. *Arch Intern Med* 1991;**151**:389-92.
- 20 Reitblat T, Drogenikov T, Sigalov I, Oren S, London D. Transient anticardiolipin antibody syndrome in a patient with parvovirus B19 infection. *Am J Med* 2000;**109**:512-13.
- 21 Suarez S, Artilles J, Balda I, Melado P, Arkuch ME, Ayala A, et al. La tuberculosis como factor de riesgo de trombosis venosa. *An Med Inter (Madrid)* 1993;**10**:398-400.
- 22 Labarca JA, Rabagliati RM, Radrigan FJ, Rojas PP, Perez CM, Ferrer MV, et al. Antiphospholipid syndrome associated with cytomegalovirus infection: case report and review. *Clin Infect Dis* 1997;**24**:197-200.
- 23 Cappell MS, Simon T, Tiku M. Splenic infarction associated with anticardiolipin antibodies with acquired immunodeficiency syndrome. *Dig Dis Sci* 1993;**38**:1153-5.
- 24 Manco-Johnson MJ, Nuss R, Key N, Moertel C, Jacobson L, Meech S, et al. Lupus anticoagulant and protein S deficiency in children with postvaricella purpura fulminans or thrombosis. *J Pediatr* 1996;**128**:319-23.
- 25 Peyton BD, Cutler BS, Stewart FM. Spontaneous tibial artery thrombosis associated with varicella pneumonia and free protein S deficiency. *J Vasc Surg* 1998;**27**:563-7.
- 26 Puri V, Bookman A, Yeo E, Cameron R, Heathcote EJ. Antiphospholipid antibody syndrome associated with hepatitis C infection. *J Rheumatol* 1999;**26**:509-10.
- 27 Uthman I, Tabbarah Z, Gharavi AE. Hughes syndrome associated with cytomegalovirus infection. *Lupus* 1999;**8**:775-7.
- 28 Viseux V, Darnige L, Carmi E, Chaby G, Poulain JF, Cevallos R, et al. Pulmonary embolism and transitory anti-beta2-GPI antibodies in an adult with chicken pox. *Lupus* 2000;**9**:558-60.
- 29 Leder AN, Flansbaum B, Zandman-Goddard G, Asherson R, Shoenfeld Y. Antiphospholipid syndrome induced by HIV. *Lupus* 2001;**10**:370-4.
- 30 Uthman T, Taher A, Khalil I. Hughes syndrome associated with varicella infection. *Rheumatol Int* 2001;**20**:167-8.
- 31 Creamer D, Hunt BJ, Black MM. Widespread cutaneous necrosis occurring in association with the antiphospholipid syndrome: a report of two cases. *Br J Dermatol* 2000;**142**:1199-203.
- 32 Baid S, Pascual M, Williams WW, Tolkoff-Rubin N, Johnson SM, Collins B, et al. Renal thrombotic microangiopathy associated with anticardiolipin antibodies in hepatitis C-positive renal allograft recipients. *J Am Soc Nephrol* 1999;**10**:146-53.
- 33 Casanova-Roman M, Rios J, Sanchez-Porto A, Casanova-Bellido M. Deep venous thrombosis associated with pulmonary tuberculosis and transient protein S deficiency. *Scand J Infect Dis* 2002;**34**:393-4.
- 34 Prieto J, Yuste JR, Beloqui O, Civeira MP, Riezu JI, Aguirre B, et al. Anticardiolipin antibodies in chronic hepatitis C: implication of hepatitis C virus as the cause of the antiphospholipid syndrome. *Hepatology* 1996;**23**:199-204.
- 35 D'Angelo A, Della Valle P, Crippa L, Patarini E, Grimaldi LM, Viganò D'Angelo S. Brief report: autoimmune protein S deficiency in a boy with severe thromboembolic disease. *N Engl J Med* 1993;**328**:1753-7.
- 36 Levin M, Eley BS, Louis J, Cohen H, Young L, Heyderman RS. Postinfectious purpura fulminans caused by an autoantibody directed against protein S. *J Pediatr* 1995;**127**:355-63.
- 37 Becker DM, Saunders TJ, Wispelway B, Schain DC. Case report: venous thromboembolism in AIDS. *Am J Med Sci* 1992;**303**:395-7.
- 38 Chevalier X, Larget-Piet B, Hernigou P, Gherardi R. Avascular necrosis of the femoral head in HIV-infected patients. *J Bone Joint Surg Br* 1993;**75B**:160.
- 39 Belmonte MA, García-Portales R, Domenech I, Fernandez-Nebro A, Camps MT, De Ramon E. Avascular necrosis of bone in human immunodeficiency virus infection and antiphospholipid antibodies. *J Rheumatol* 1993;**20**:1424-8.
- 40 Malnick SD, Abend Y, Evron E, Stoeber ZM. HCV hepatitis associated with anticardiolipin antibody and a cerebrovascular accident. Response to interferon therapy. *J Clin Gastroenterol* 1997;**24**:40-2.
- 41 Gibson GE, Gibson LE, Drage LA, Garrett CR, Gertz MA. Skin necrosis secondary to low-molecular weight heparin in a patient with antiphospholipid antibody syndrome. *J Am Acad Dermatol* 1997;**37**:855-9.
- 42 Olive A, Queralt C, Sierra G, Centelles M, Force L. Osteonecrosis and HIV infection: Osteonecrosis and HIV infection. *J Rheumatol* 1998;**25**:1243-4.
- 43 Cailleux N, Marie I, Jeanton M, Lecomte F, Levesque H, Courtois H. Are antiphospholipid antibodies pathogenic in the course of human immunodeficiency virus infection? *J Mal Vasc* 1999;**24**:53-6.
- 44 Yañez A, Cedillo L, Neyrolles O, Alonso E, Alonso E, Prevost MC, Rojas J, et al. Mycoplasma penetrans bacteremia and primary antiphospholipid syndrome. *Emerg Infect Dis* 1999;**5**:164-7.
- 45 Padovan CS, Pfister HW, Bense S, Fingerle V, Abele-Horn M. Detection of Mycoplasma pneumoniae DNA in cerebrospinal fluid of a patient with M. pneumoniae infection-"associated" stroke. *Clin Infect Dis* 2001;**33**:E119-21.
- 46 Korkmaz C, Harmanci E, Metintas I, Gulbas Z. Antiphospholipid syndrome associated with intestinal amoebiasis. *Scand J Infect Dis* 2001;**33**:938-40.
- 47 Nakajima T, Kitahara H, Kono T, Ohta K, Takano T, Hasegawa R, et al. A surgical case of acute aortic dissection with antiphospholipid syndrome. *Jpn J Cardiovasc Surg* 2001;**30**:311-13.
- 48 Turhal NS, Peters VB, Rand JH. Antiphospholipid syndrome in HIV infection - report on four cases and review of the literature. *Acta Internat* 2001;**13**:268-71.
- 49 Brown P, Crane L. Avascular necrosis of bone in patients with human immunodeficiency virus infection: report of 6 cases and review of the literature. *Clin Infect Dis* 2001;**32**:1221-6.
- 50 Ehrenfeld M, Bar-Natan M, Sidi Y, Schwartz E. Antiphospholipid antibodies associated with severe malaria infection [abstract]. *Lupus* 2002;**11**:S611.
- 51 Roldan R, Perez-Guijo V, Anton M, Castro C, Collantes E. Two new cases of catastrophic APS in pediatric patients [abstract]. *Lupus* 2002;**11**:S618.
- 52 Cervera R, Gómez-Puerta JA, Espinosa G, Font J, De Pa Red G, Gil V, et al. "CAPS Registry": a review of 200 cases from the International Registry of patients with catastrophic antiphospholipid syndrome (CAPS) [abstract]. *Ann Rheum Dis* 2003;**62**(suppl 1):88.
- 53 Olguin-Ortega L, Jara LJ, Becerra M, Ariza R, Espinosa L, Wilson W, et al. Neurological involvement as a poor prognostic factor in catastrophic antiphospholipid syndrome: autopsy findings in 12 cases. *Lupus* 2003;**12**:93-8.
- 54 Koschmieder S, Miesbach W, Fauth F, Bojunga J, Scharrer I, Brodt HR. Combined plasmapheresis and immunosuppression as a rescue treatment of a patient with catastrophic antiphospholipid syndrome. *Blood Coagul Fibrinolysis* 2003;**14**:395-9.
- 55 Villamil A, Sorkin E, Basta MC, Mysler E, Macias S, Pekolj J, et al. Catastrophic antiphospholipid syndrome complicating orthotopic liver transplantation. *Lupus* 2003;**12**:140-3.
- 56 Tattevin P, Dupeux S, Hoff J. Leptospirosis and the antiphospholipid syndrome. *Am J Med* 2003;**114**:164.
- 57 Wasserman A. Über Entwicklung und den Gegenwartigen Stand der Serodiagnostik Gegenüber Syphilis. *Berl Klin Wochenschr* 1907;**44**:1599-634.
- 58 Machelis L. Precipitin reaction bei syphilis. *Berl Klin Wochenschr* 1907;**44**.
- 59 Harris EN, Gharavi AE, Boey ML, Patel BM, Mackworth-Young CG, Loizou S, et al. Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. *Lancet* 1983;**ii**:1211-14.
- 60 Harris EN, Baguley E, Asherson RA, Hughes GRVH. Clinical and serological features of the "antiphospholipid syndrome" [abstract]. *Br J Rheumatol* 1987;**26**:19.
- 61 Galli M, Comfurios P, Maassen C, Hemker HC, de Baets MH, van Breda-Vriesman PJ, et al. Anticardiolipin antibodies (ACA) directed not to cardiolipin but to a plasma protein cofactor. *Lancet* 1990;**335**:1544-7.
- 62 McNeil HP, Simpson RJ, Chesterman CN, Krilis SA. Anti-phospholipid antibodies are directed against a complex antigen that includes a lipid-binding inhibitor of coagulation, β_2 -glycoprotein 1 (apolipoprotein H). *Proc Natl Acad Sci USA* 1990;**87**:4120-4.
- 63 Matsuura E, Igarashi Y, Fujimoto M, Ichikawa K, Koike T. Anticardiolipin cofactor(s) and differential diagnosis of autoimmune disease [letter]. *Lancet* 1990;**336**:177-8.
- 64 Hunt JE, McNeil HP, Morgan GJ, Cramer IR, Krilis SA. A phospholipid B-B2-glycoprotein I complex is an antigen for anticardiolipin antibodies occurring in autoimmune disease but not with infection. *Lupus* 1992;**1**:75-81.
- 65 Elbeily A, Strassburger-Larna K, Atsumi T, Bertolaccini ML, Amengual O, Hanafi M, et al. Antiphospholipid antibodies in leprotic patients: a correlation with disease manifestations. *Clin Exp Rheumatol* 2000;**18**:492-4.
- 66 Hojnik M, Gilburd B, Ziporen L, Blank M, Tomer Y, Scheinberg MA, et al. Anticardiolipin antibodies are heterogeneous in their dependency on B2-glycoprotein 1: analysis of anticardiolipin antibodies in leprosy. *Lupus* 1994;**3**:515-21.
- 67 Fiallo P, Nunzi E, Cardo PP. Beta2 glycoprotein-1-dependent anticardiolipin antibodies as risk factors for reactions in borderline leprosy patients. *Int J Lepr Other Mycobact Dis* 1998;**66**:387-8.

- 68 **Loizou S**, Cazabon JK, Walport MJ, Tait D, So AK. Similarities of specificity and cofactor dependence in serum antiphospholipid antibodies from patients with human parvovirus B19 infection and those with systemic lupus erythematosus. *Arthritis Rheum* 1997;**40**:103–8.
- 69 **Oldstone MB**. Molecular mimicry and immune-mediated diseases. *FASEB J* 1998;**80**:355–77.
- 70 **Karlsen AE**, Dyrberg T. Molecular mimicry between non-self, modified self and self in autoimmunity. *Semin Immunol* 1998;**10**:25–34.
- 71 **Albert LJ**, Inman RD. Molecular mimicry and autoimmunity. *N Engl J Med* 1999;**341**:2068–74.
- 72 **Blank M**, Krause I, Fridkin M, Keller N, Kopolovic J, Goldberg I, et al. Bacterial induction of autoantibodies to β 2-glycoprotein-1 accounts for the infectious etiology of antiphospholipid syndrome. *J Clin Invest* 2002;**109**:797–804.
- 73 **Zhang I**, Jaconsson K, Strom K, Lundberg M, Frykberg KL. Staphylococcus aureus expresses a cell surface protein that binds both IgG and B2-glycoprotein 1. *Microbiology* 1999;**145**:177–83.
- 74 **Gharavi EE**, Chaimovich H, Cucurull E, Celli CM, Tang H, Wilson WA, et al. Induction of antiphospholipid antibodies by immunization with synthetic viral and bacterial peptides. *Lupus* 1999;**8**:449–55.
- 75 **Gharavi AE**, Pierangeli SS, Espinola RG, Liu X, Coden-Stanfield M, Harris EN. Antiphospholipid antibodies induced in mice by immunization with a cytomegalovirus-derived peptide cause thrombosis and activation of endothelial cells in vivo. *Arthritis Rheum* 2002;**46**:545–52.
- 76 **Ordi-Ros J**, Villarreal J, Monegal F, Sauleda S, Estaban I, Vilardell M. Anticardiolipin antibodies in patients with chronic hepatitis C infection characterization in relation to antiphospholipid syndrome. *Clin Diagn Lab Immunol* 2000;**7**:241–4.
- 77 **Dalekos GN**, Kistis KG, Boumba DS, Voulgari P, Zervou EK, Drosos AA, et al. Increased incidence of anti-cardiolipin antibodies in patients with hepatitis C is not associated with aetiopathogenic link to antiphospholipid syndrome. *Eur J Gastroenterol Hepatol* 2000;**12**:67–74.
- 78 **Sthoeger ZM**, Fogel M, Smirov A, Ergas D, Lurie Y, Bass DD, et al. Anticardiolipin autoantibodies in serum samples and cryoglobulins of patients with chronic hepatitis C infection. *Ann Rheum Dis* 2000;**59**:483–6.
- 79 **Cacoub P**, Renou C, Rosenthal E, Cohen P, Loury I, Loustaud-Ratti V, et al. Extrahepatic manifestations associated with hepatitis C infection. A prospective multicentre study of 321 patients. *Medicine (Baltimore)* 2000;**79**:45–56.
- 80 **Muñoz-Rodríguez FJ**, Tàssies D, Font J, Reverter JC, Cervera R, Sánchez-Tapias JM, et al. Prevalence of hepatitis C virus infection in patients with antiphospholipid syndrome. *J Hepatol* 1999;**30**:770–3.
- 81 **Giordano P**, Galli M, Del Vecchio GC, Altomare M, Norbis F, Ruggeri L, et al. Lupus anticoagulant anticardiolipin antibodies and hepatitis C infection in thalassaemia. *Br J Haematol* 1998;**102**:903–6.
- 82 **Yamazaki M**, Asakura H, Kawamura Y, Ohka T, Endo M, Matsuda T. Transient lupus anticoagulant induced by Epstein-Barr virus infection. *Blood Coagul Fibrinolysis* 1991;**2**:771–4.
- 83 **Barcat D**, Constans J, Seigneur M, Guerin V, Conn C. Thrombose veineuse profonde contemporaine d'une varicelle de l'adulte. *Rev Med Interne* 1998;**27**:563–7.
- 84 **Faghiri Z**, Wilson WA, Taheri P, Barton EN, Morgan OS, Gharavi AE. Antibodies to cardiolipin and beta-2 glycoprotein 1 in HTLV-1-associated myelopathy/tropical spastic paraparesis. *Lupus* 1999;**8**:210–14.
- 85 **Bloom EJ**, Abrams DI, Rodgers G. Lupus anticoagulant in the acquired immunodeficiency syndrome. *JAMA* 1986;**258**:491–3.
- 86 **Asherson RA**, Shoenfeld Y. Human immunodeficiency virus infection, antiphospholipid antibodies, and the antiphospholipid syndrome. *J Rheumatol* 2003;**30**:214–19.
- 87 **Argov S**, Shattner Y, Burstein R, Handzel ZT, Shoenfeld Y. Autoantibodies in male homosexuals and HIV infection. *Immunol Lett* 1991;**30**:31–6.
- 88 **Coll J**, Gutierrez-Cebollada J, Yazbeck H, Berges A, Rubies-Prat J. Anticardiolipin antibodies and acquired immunodeficiency syndrome: prognostic marker or association with HIV infection? *Infection* 1992;**20**:140–2.
- 89 **Fiallo P**, Travaglio C, Nunzi E, Cardo PP. Beta-2 glycoprotein dependence of anticardiolipin antibodies in multibacillary leprosy patients. *Lepr Rev* 1998;**69**:376–81.
- 90 **Levy RA**, Pierangeli SA, Espinola RG. Antiphospholipid beta-2 glycoprotein 1 dependency assay to determine antibody pathogenicity [abstract]. *Arthritis Rheum* 2000;**43s**:1476.
- 91 **Espinosa G**, Santos E, Cervera R, Piette JC, de la Red G, Gil V, et al. Adrenal involvement in the antiphospholipid syndrome: clinical and immunologic characteristics of 86 patients. *Medicine (Baltimore)* 2003;**82**:106–18.
- 92 **Asherson RA**. The catastrophic antiphospholipid syndrome. *J Rheumatol* 1992;**19**:508–12.
- 93 **Asherson RA**. The pathogenesis of the catastrophic antiphospholipid syndrome. *J Clin Rheumatol* 1999;**4**:249–52.
- 94 **Uhtman I**, Taher A, Khalil I, Bizriou AR, Gharavi AE. Catastrophic antiphospholipid syndrome associated with typhoid fever. Comment on the article by Hayem et al. *Arthritis Rheum* 2002;**46**:850.
- 95 **Asherson RA**, Cervera R, de Groot PG, Erkan D, Boffa MC, Piette JC, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus* 2003;**12**:530–4.
- 96 **Asherson RA**, Shoenfeld Y. The role of infection in the pathogenesis of catastrophic antiphospholipid syndrome – molecular mimicry? *J Rheumatol* 2000;**27**:12–14.
- 97 **Annane D**, Sébille V, Charpentier C, Bollaert PE, Francois B, Korach JM, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;**288**:862–71.