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Presence of Antibodies Against *Mycoplasma penetrans* in Patients with Antiphospholipid Syndrome

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1. Introduction

The etiology of autoimmune diseases is multifactorial. The degree to which genetic and environmental factors influence susceptibility to autoimmune diseases is not fully understood. The antiphospholipid syndrome (APS) is characterized by vascular thrombosis, and/or pregnancy morbidity associated with anticardiolipin (aCL), anti- β 2-glycoprotein-I (anti- β 2-GPI) and lupus anticoagulant (LAC). [Levy et al., 2006].

1.1 Antiphospholipid syndrome

Antiphospholipid syndrome (APS), first described between 1983 to 1986, is characterized by a wide variety of hemocytopenic and vaso-occlusive manifestations and is associated with antibodies directed against negatively charged phospholipids. Features of APS include hemolytic anemia, thrombocytopenia, venous and arterial occlusions, livedo reticularis, pulmonary manifestations, recurrent fetal loss, neurologic manifestations (stroke, transverse myelitis, Guillain-Barré syndrome); and a positive Coombs test, anticardiolipin antibodies, or lupus anticoagulant activity. The factor(s) causing production of the antiphospholipid antibodies in primary antiphospholipid syndrome (PAPS) remain unidentified. [Hughes, 1993; Asherson et al., 1994; Yáñez et al., 1999].

2. Mycoplasmas

Mycoplasmas are eubacteria included within the Class Mollicutes, which comprises the smallest self-replicating bacteria, showing distinctive features such as: a) lack of a rigid cell wall envelope, b) sterol incorporation into their own plasma membrane, and c) reduced cellular (0.3 - 0.8 μm diameter) and genome sizes (0.58-2.20 Mb). [Bove, 1993; Razin et al., 1998]. Due to their reduced genome sizes, mycoplasmas exhibit restricted metabolic and physiological pathways for replication and survival [Razin et al., 1998]. Thus it is evident why these bacteria display strict dependence to their hosts for acquisition of aminoacids, nucleotides, lipids and sterols as biosynthetic precursors. [Baseman & Tully, 1997; Razin et al., 1998]. Currently, there are more than 200 species allocated into four orders, five families and eight genera within the Class Mollicutes [Brown et al., 2007]. All species of Mycoplasmataceae are obligate parasites and host specificity is quite strict for hosts including humans, rodents and birds. Mycoplasmal infections are most frequently associated with disease in the urogenital or respiratory tracts and, in most cases, mycoplasmas infect the host persistently. Like other parasites, many mycoplasma species display antigenic diversity, which has been noted in a variety of protein profiles or colony immunoblotting. [Sasaki, 2002].

2.1 Immune response against mycoplasmas

Host defense in mycoplasmal disease is dependent on both innate and humoral immunity. [Waites & Atkinson, 2009]. Molecular mimicry, survival within cells and phenotypic plasticity (antigenic variation) are the major mechanisms by which mycoplasmas evade the immune response [Chambaud et al, 1999; Razin et al., 1998; Rottem & Naot, 1998]. Association between immunodeficiency and mycoplasmal infections has been reported since the mid 1970s. Mycoplasmas can disseminate from localized infections and cause invasive diseases, especially in hypogammaglobulinemic subjects. [Cassell et al., 1994]. Antigenic variation is considered to be a strategy for persistence in the face of immune responses by the host. [Sasaki, 2002].

2.2 Diagnostic procedures

Many mycoplasmal diseases are quite different than those for fast-growing bacteria. It is noteworthy that mycoplasmal etiology of respiratory diseases is considered only after failure of diagnosis of other common bacterial etiologies. In addition, there are few specialized or reference laboratories and skilled personnel [Cassell et al., 1994; Waites & Atkinson, 2009]. PCR testing for species-specific mycoplasmal infection is suitable for clinical diagnosis. A culture enhanced PCR approach has also been suggested to overcome the effect of inhibitors in the amplification process [Abele-Horne et al., 1998].

2.3 Treatment

Due to absence of the cell wall envelope, mycoplasmas are insensitive to β -lactam antibiotics. However, antibiotics targeting protein synthesis or DNA modification molecules are highly effective against these bacteria. Macrolides, tetracyclines and fluoroquinolones eliminate mycoplasmas efficiently both *in vivo* and *in vitro* [Cassell et al., 1994; Waites & Atkinson, 2009].

3. *Mycoplasma penetrans*

Mycoplasma penetrans infects humans in the urogenital and respiratory tracts. A typical feature of *Mycoplasma penetrans* is its penetration into human cells. Internalization of the organisms into the urothelium was detected in autopsy samples from an acquired immunodeficiency syndrome (AIDS) patient [Lo, et al., 1992]. Intracellular replication and persistence for at least 6 months has been observed in cultured cells. [Dallo, et al., 2000].

Mycoplasma penetrans was first isolated from urine of homosexual men infected with (HIV), but not from healthy age-matched subjects. Subsequent studies suggested an association of this mycoplasma with Kaposi's sarcoma, but later findings did not confirm such association. [Baseman & Tully, 1997].

In humans, *Mycoplasma penetrans* is associated mainly with HIV-1 infection, particularly in adults among the homosexual population in Europe and the USA, and among both homosexual and heterosexual males in South America. Anti- *Mycoplasma penetrans* antibodies are found even in asymptomatic HIV carriers and in patients in the process of developing AIDS [Lo, S.C. et al., 1992; Cordova, et al., 1999; Grau, et al. 1995; Lo, et al. 1991; Lo, et al. 1992, Lo, et al. 1993; Wang, et al. 1992; Wang, et al., 1993]. Both the rapid decline in CD4-positive lymphocyte counts in *Mycoplasma penetrans* -seropositive HIV-infected individuals and the mitogenic effects of this organism on lymphocytes imply a contribution of persistent *Mycoplasma penetrans* infection to the deterioration of the immune system in HIV infection. [Grau, et al. 1998; Sasaki, et al., 1995]

On the other hand, *Mycoplasma penetrans* infection has also been suggested to be a primary cause of human disease in non-HIV-related urethritis and respiratory disease. [Cordova, et al, 1999; Yáñez et al. 1999] The *Mycoplasma penetrans* HF-2 strain was isolated from a previously healthy HIV-negative patient suffering from severe respiratory distress caused by *Mycoplasma penetrans* infection-associated systemic disease. [Yáñez et al. 1999]

The *Mycoplasma penetrans* HF-2 strain possesses a 1.3 Mb genome, which is the largest among the Mycoplasmataceae species thus far analyzed. Sasaki et al., identified 1038 putative coding DNA sequences (CDSs), among which 463 are *Mycoplasma penetrans* specific. The relatively large *Mycoplasma penetrans* genome compared with other mycoplasma genomes may be accounted for a probably rich core proteome. This data should be of great use for understanding the mechanism of *Mycoplasma penetrans* infection of humans and will also provide new insights into the regulation of virulence factors in *Mycoplasma penetrans* as well as other Mycoplasmataceae. [Sasaki, 2002].

4. Objective

The aim of this study was to determine the presence of antibodies against *Mycoplasma penetrans* in patients with antiphospholipid Syndrome.

5. Material and methods

5.1 Subjects

Eighty-eight patients at the Rheumatology Service of the "Hospital Manuel Avila Camacho del Instituto Mexicano del Seguro Social" in Puebla City, Mexico were included in the study.

A rheumatologist examined the patients and all fulfilled the American College Rheumatology criteria. Eighteen patients were diagnosed with Primary Antiphospholipid Syndrome, 26 patients with Secondary Antiphospholipid Syndrome and 44 patients with Systemic Lupus Erythematosus (SLE).

Forty four women without any autoimmune or infectious disease were included in the study as healthy women. Healthy women were not under antibiotic or drug treatment. The ethics committee of the Hospital approved this study and informed patient consent was obtained.

5.2 Specimens

Peripheral whole blood samples from patients and healthy women were collected in order to detect IgG, IgM and IgA antibodies against cardiolipin and β 2 glycoprotein I using a ELISA Test. Immunoglobulin M and G against *Mycoplasma penetrans* were also investigated using ELISA and Western blot assays. Blood samples were collected in tubes without anticoagulant and stored at -20°C until use.

5.3 Detection of antibodies anticardiolipin using ELISA test

Antibodies anticardiolipin and anti- β 2 glycoprotein I were tested in all patients and healthy persons. Diagnostic Automation Inc. ELISA test was used to detect IgG, IgA and IgM against cardiolipin and β 2 glycoprotein I.

5.4 Detection of antibodies against *Mycoplasma penetrans* by ELISA test

Mycoplasma penetrans HF strain was cultured in E media, centrifuged at 12,000 rpm for 40 min and suspended in PBS (0.015 M pH 7.4). This procedure was repeated 3 times until the suspension was adjusted to an $\text{OD}_{600} = 1$ using a carbonate buffer (0.1M pH 9.6). This suspension was considered the antigen. Two hundred microliters of antigen was added to each well of the plate. The plates were covered and incubated at 37°C for two hours. The plates were kept at 4°C for 4 days before use and antigen excess was removed. The plates were washed five times with PBS and then dried. Two hundred microliters of 2 % skim milk diluted in PBS-Tween 0.05% were added to each well of the plate. Plates were covered and kept at 4°C for one night, then, excess skim milk was removed. Two hundred microliters of patient's sera diluted 1:200 in PBS-Tween 0.05% were added to each well plate and incubated at room temperature during night. Antihuman IgM or IgG alkaline-phosphatase conjugates diluted 1:1000 were added and incubated at room temperature for one hour. The conjugate was removed and the plates were washed five times with PBS/Tween (0.05 %). Two hundred microliters of alkaline phosphatase substrate was added to each well. These plates were incubated in the dark until a yellow color was visible and reaction was stopped adding 20 microliters of Na OH 1N in each well. Plates were read at 405 nm in a multiscan ELISA meter. Positive and negative controls were tested.

5.5 Detection of antibodies against *Mycoplasma penetrans* using Western Blot tests

Mycoplasma penetrans HF whole cell was used as an antigen. The bacteria was cultured in E media, centrifuged at 12,000 rpm for 40 min and suspended in PBS (0.015 M pH 7.4). This

procedure was repeated 3 times until the suspension was adjusted to an $OD_{600} = 1$ using PBS and 750 microliters of this solution was mixed with 250 microliters of sample buffer (40 % glycerol, 240 mM Tris/HCl pH 6.8, 0.04% bromophenol blue, 5 % β -mercaptoethanol and boiled during 10 minutes. A 14 % PAGE-SDS gel was used in order to separate proteins using 100 volts for 3 hours. The proteins were transferred to nitrocellulose (0.45 nm pore). Transfers were done using a semidry chamber at 15 volts for 15 minutes. Membranes were stained using amido black to verify proteins transference. The membranes were blocked using a 2% skim milk solution for 1 hour at room temperature. The IgM and IgG antibodies against *Mycoplasma penetrans* were detected using 2 nitrocellulose 5 mm wide strips in each patient's serum diluted 1:50 in PBS. The strips were stirred constantly for 1 hour at room temperature and washed 5 times with PBS-Tween (0.05%). Each strip was in contact with the alkaline phosphatase conjugate (anti-human IgM or IgG) for 1 hour at room temperature. The strips were washed five times with PBS-Tween (0.05%) and presence of antibodies was detected with a mixture of 66 microliters of nitro blue tetrazolium (NTB), 33 microliters of 5-bromo-4-cloro-3-indolilphosphate (BCIP), and 10 microliters of alkaline phosphatase buffer.

5.6 Environmental data collection

Patients and healthy people were questioned about environmental factors (living conditions, presence of pets at home, presence of rivers, garbage dumps or standing water, use of insecticide, presence of preeclampsia, infectious diseases and their medical history).

6. Results

Eighty eight patients were included in the study, 18 patients were diagnosed with Primary Antiphospholipid Syndrome (APS), 26 patients with Secondary Antiphospholipid Syndrome and 44 patients with Systemic Lupus Erythematosus. All patients were females whose age ranged from 13 to 64 years old.

6.1 Anticardiolipin antibodies

Five patients with Primary APS tested positive for anticardiolipin and anti- $\beta 2$ glycoprotein I (5/18), five patients with Secondary APS tested positive (5/26) in remained 13 Primary APS and 21 Secondary APS patients, lupus anticoagulant were present. Two patients with SLE (2/44), none of the healthy persons were positive (0/44) for anticardiolipin and anti- $\beta 2$ glycoprotein I antibodies. X^2 was calculated and it showed an association between anticardiolipin antibodies and primary APS ($p = 0.006$)

6.2 Detection of antibodies against *Mycoplasma penetrans* by ELISA

Antibodies against <i>Mycoplasma penetrans</i>	Primary APS	Secondary APS	SLE	Healthy Persons
Ig G	8/18 (44 %)	20/26 (77%)	20/44 (45%)	2/44 (4%)
Ig M	14/18 (78%)	22/26 (85%)	33/44 (75%)	2/44 (4%)

X^2 was calculated, there was an association between presence of both Ig G and IgM antibodies with Secondary APS

6.3 Detection of antibodies against *Mycoplasma penetrans* using Western Blot

Antibodies against <i>Mycoplasma penetrans</i>	Primary APS	Secondary APS	SLE	Healthy Persons
Ig G	13/18 (72%)	11/19 (55%)	13/24 (54%)	2/44 (4%)
Ig M	13/18 (72%)	13/19 (68%)	16/24 (67%)	2/44 (4%)

χ^2 was calculated $p > 0.05$. There was no association between the development of antibodies and disease.

We performed first the detection of antibodies using ELISA test and then using Western Blot test. Unfortunately we did not have enough serum from 7 patients with Secondary APS and 20 patients with SLE and we could not contact them to get more sample.

6.4 Presence of antibodies in patients and controls

Antibody	Primary APS	Secondary APS	SLE	Healthy persons
Anticardiolipin and Anti- β 2 glycoprotein I	6/18 (33%)	5/26 (19%)	2/44 (4%)	0/44 (0%)
IgG vs <i>Mycoplasma penetrans</i> (ELISA)	8/18 (44%)	20/26 (77%)	20/44 (45%)	2/44 (4%)
IgM vs <i>Mycoplasma penetrans</i> (ELISA)	14/18 (78%)	22/26 (85%)	33/44 (75%)	2/44 (4%)
IgG vs. <i>Mycoplasma penetrans</i> (Western blot)	3/18 (72%)	11/19 (55%)	13/24 (54%)	2/44 (4%)
IgM vs. <i>Mycoplasma penetrans</i> (Western blot)	3/18 (72%)	13/19 (68%)	16/24 (67%)	2/44 (4%)

χ^2 was calculated $p < 0.0007$. There was an association between presence of antibodies only in patients with APS and SLE.

6.5 Presence of environmental factors

Environmental Factors	Primary APS	Secondary APS	SLE	Healthy Persons
Lack of running water, electricity and sewage system	1/18 (5%)	5/26 (19%)	1/44 (2%)	3/44 (7%)
More than 3 people sleeping in the same room	1/18 (5%)	3/26 (11%)	11/44 (25%)	8/44 (18%)
Presence of pets (dogs, cats and birds) at home	11/18 (61%)	13/26 (50%)	30/44 (68%)	30/44 (68%)
Presence of rivers, garbage dumps or standing water near their houses	8/18 (44%)	12/26 (46%)	22/44 (50%)	15/44 (34%)
Frequent use of insecticide	6/18 (33%)	11/26 (42%)	13/44 (30%)	16/44 (36%)

Environmental Factors	Primary APS	Secondary APS	SLE	Healthy Persons
Preeclampsia	1/18 (5%)	4/26 (15%)	6/44 (14%)	6/44 (14%)
Common presence of infectious diseases	8/18 (44%)	8/26 (31%)	23/44 (52%)	1/44 (2%)
Seasonal aggravation of symptoms	13/18 (72%)	12/26 (46%)	32/44 (72%)	0/44 (0%)
Family medical history of rheumatic diseases	3/18 (17%)	10/26 (38%)	18/44 (41%)	3/44 (7%)

X² was calculated p<0.0001. There was an association between presence of some environmental factors and disease.

7. Discussion

The etiology and pathogenesis of most autoimmune diseases, including the APS, remain unclear, with the involvement of infectious, autoimmune, and auto inflammatory pathways possibly being implicated. Infection may initiate a disease, although it is the combination of genetic regulation in the host, the interplay between virus or bacteria persistence, and autoimmunity that produces the later phases of disease, the antigenic determinants responsible for inducing autoimmune disease, and the pathogenic effector mechanisms. [Garcia-Carrasco et al., 2009].

Cervera et al., analyzed the clinical characteristics of 100 patients with antiphospholipid syndrome (APS) associated with infections. The main clinical manifestations of APS included: pulmonary involvement (39%), skin involvement (36%), and renal involvement (35%); nine with renal thrombotic microangiopathy. The main associated infections and agents included skin infection (18%), HIV (17%), pneumonia (14%), hepatitis C (13%), and urinary tract infection (10%). They concluded that various different infections can be associated with thrombotic events in patients with APS, including the potentially lethal subset termed catastrophic APS. [Cervera et al., 2004].

Infectious agents can play a dual role in the etiopathogeny of APS, acting as the initial trigger of the production of antibodies cross-reacting with β 2 glycoprotein I (β 2GPI) and infectious peptides, and also inducing an inflammatory response. This is the so-called "two-hit theory" in which pathogenic anti- β 2GPI antibodies act as the first hit and inflammatory responses as the second. [Amital et al. 2008; García-Carrasco et al. 2009].

Antiphospholipid antibodies (aPL) may be demonstrated during the course of many infections in addition to occurring in conditions such as Systemic Lupus Erythematosus (SLE), APS, and a wide variety of other rheumatic diseases. Syphilis was the first infection to be linked with aPL: one of the components of the VDRL reagent (cardiolipin) being responsible for the original finding that antibodies thought initially to be directed against cardiolipin were, in fact, pivotal in the pathogenesis and for the diagnosis of the APS. [Asherson, R.A., & Shoenfield, Y., 2003].

Interestingly, it has been reported that a substantial number of patients with *Mycoplasma pneumoniae*-induced respiratory disease have anticardiolipin antibodies. Furthermore, many

clinical criteria for APS have also been well documented in patients with *M. pneumoniae* infection, including Guillain-Barré-like illness and other central nervous system manifestations, hemolytic anemia, positive Coombs test, thrombocytopenia, and arthritis. [Asherson et al., 1994; Snowden et al., 1990; Yáñez et al., 1999].

Snowden et al. (1990) found antiphospholipid antibodies in more than 50% of patients with *M. pneumoniae* pneumonia, especially those with severe infections requiring hospitalization. Catteau et al., described two cases of Stevens-Johnson syndrome associated with *M. pneumoniae* infection and the presence of antiphospholipid antibodies. [Snowden et al., 1990; Catteau et al., 1995].

In a previous work, *Mycoplasma penetrans* was isolated from the blood and throat of a previously healthy non-HIV-infected 17-year-old woman sexually inactive who had an acute onset of arthritis, fever, and hemolytic anemia. Upon hospital admission, she developed respiratory distress, severe hemolytic anemia, leukocytosis, and thrombocytopenia. Blood and bone marrow smears did not show a neoplastic process. She was treated with methylprednisolone and trimethoprim/sulfamethoxazole on day 2, but her condition deteriorated. On day 3, the antibiotic treatment was changed to ceftazidime. On day 4 severe respiratory distress and hypoxemia developed, and the patient was admitted to the intensive care unit. Venereal Disease Research Laboratory (VDRL) tests were negative as were tests for Systemic Lupus Erythematosus. The patient was shown to have anti-dsDNA antibodies but positive anticardiolipin antibodies by ELISA test. Respiratory secretions were culture-negative and were shown to be negative by immunofluorescence for respiratory syncytial virus, adenovirus, influenza A, influenza B, parainfluenza 1,2,3, and *Chlamydia*. Serologic analysis indicated that the patient had no antibodies against HIV, hepatitis B or C virus. No acid-fast bacilli or other bacteria were observed on blood and tracheal aspirate smears. In addition, thoracic radiography showed only bilateral diffuse pulmonary infiltrates. On day 2 of hospital admission, blood and throat samples were cultured for aerobic flora and mycoplasma. *Mycoplasma penetrans* was isolated in a pure culture from the patient's blood (isolate HF-1) and throat (isolate HF-3). Later *Mycoplasma penetrans* was isolated from tracheal aspirate in pure culture (isolate HF-2). Treatment was initiated on day 6 with clindamycin and vancomycin. The patient also received transfusion of two units of washed red blood cells. After 3 days of treatment, the patient improved clinically and was released from the intensive care unit on day 9; thoracic radiographs were clear. [Yáñez et al., 1999].

Mycoplasma penetrans infection was detected in the APS patient's specimens prior to culture and was confirmed by specific polymerase chain reaction (PCR). Similar results were obtained by another pair of PCR primers also within the 16S rRNA gene and designed for the specific detection of *Mycoplasma penetrans*. Samples from both original specimens and broth cultures were tested by PCR for other human mycoplasmas, but none were detected. This finding was the basis of our present study, where the main purpose was to determine if the presence of *Mycoplasma penetrans* is a casual event or the bacteria may play a role in the pathogenesis of APS and SLE. [Yáñez et al., 1999].

Since autoimmune diseases may be influenced by environmental factors, we questioned patients about the presence of these factors. Some aspects about the epidemiology and pathogenesis of *Mycoplasma penetrans* infections remain unknown, so some questions try to

search for the primary habitat of the bacteria and others about the contact of the patients with some environmental factors that may influence the development of APS and SLE. [Yáñez et al., 1999].

Mycoplasmas are the smallest free living microorganisms and also defined as fastidious bacteria because of their nutritional requirements that is why the detection used immunological techniques to determine if the presence of antibodies anti- *Mycoplasma penetrans* are common in patients with APS and SLE but they are absent or in a low proportion of healthy people. IgG and IgM antibodies were detected suggesting a recent infection in the patient and/or a permanent contact of the bacteria with the host. Most patients were under corticosteroid or immunosuppressive therapy. These treatments may favor the persistence of *Mycoplasma penetrans* in patients with APS and SLE. [Yáñez et al., 1999].

The presence of *Mycoplasma penetrans* may not be casual and it could favor the development of APS or SLE. *Mycoplasma penetrans* is able to produce Phospholipase A2. This enzyme degrades the phospholipids of the host membrane and helps *Mycoplasma penetrans* in the penetration to the host cell [Salman, et al., 1998; Rottem, S., 2003]. It is well known that mycoplasmas induce autoimmune diseases in appropriate hosts. [Baseman & Tully, 1997; Waites & Atkinson, 2009]. Previous studies suggest that mycoplasmas may induce antiphospholipid antibodies [Snowden, et al., 1990; Yáñez et al., 1999]. Although there was an association between common presence of infectious diseases and seasonal aggravation of symptoms and/or APS and SLE, more studies need to be done. It was not possible to establish an association between the presence of an environmental factor and APS and SLE.

8. Conclusion

Mycoplasma penetrans was first reported in 1993 as an emerging infectious agent. Yáñez et al., 1999 reported the first of *Mycoplasma penetrans* isolation in a non-HIV-infected patient with APS. The mycoplasma strain isolated from the APS patient exhibited typical morphologic features of *Mycoplasma penetrans*, which are unique among mycoplasmas isolated from humans. The lack of *Mycoplasma penetrans* strong humoral response in the APS patient was a factor in favor of dissemination of the mycoplasma, hence its isolation from the blood. A possible association between *Mycoplasma penetrans* and APS should be considered.

Antibodies against *Mycoplasma penetrans* in a high proportion of APS or SLE patients suggest that the presence of the bacteria is not casual and mycoplasmas may play a role in the development of these diseases.

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10. References

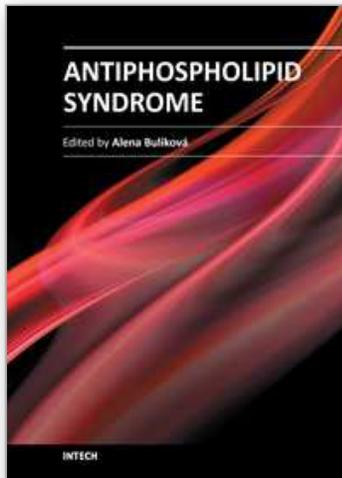
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The antiphospholipid syndrome has been described for the first time by Graham Hughes in 1983 as a condition connected with thromboses or foetal losses and antiphospholipid antibodies presence. From that time there has been a great progress in knowledge, including antiphospholipid antibodies characterisation, their probable and also possible action, clinical manifestations, laboratory detection and treatment possibilities. This book provides a wide spectrum of clinical manifestations through Chapters written by well known researchers and clinicians with a great practical experience in management of diagnostics or treatment of antiphospholipid antibodies' presence.

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