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Splenic infarction associated with transient anti-prothrombin antibodies is a rare manifestation of acute *Mycoplasma pneumoniae* infection

Short title: *Mycoplasma pneumoniae*, anti-prothrombin antibodies and splenic infarction

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ABSTRACT:

We report the first paediatric case of splenic infarction following acute *Mycoplasma pneumoniae* infection with induction of anti-prothrombin (aPT) antibodies. A 12-year-old boy was admitted to the paediatric emergency department for a left pleuropneumonia and a splenic infarction. aPT antibodies were transiently detected. The patient recovered fully after antibiotic therapy and a 3-month course of anticoagulation treatment. Antiphospholipid (aPL) antibodies induced by acute infections have already been reported but cases of clinically relevant thrombosis remain rare. The pathogenicity of aPT antibodies is discussed here. We hypothesize that these antibodies were involved in this symptomatic hypercoagulable state.

KEYWORDS:

Mycoplasma pneumoniae, antiphospholipid antibodies, anti-prothrombin antibodies, splenic infarction, thrombosis.

1. INTRODUCTION:

Mycoplasma pneumoniae is a cause of upper and lower respiratory tract infections. The most typical syndrome in children is bronchitis and tracheobronchitis. A variety of extrapulmonary manifestations have been described such as encephalitis, polyradiculitis, haemolytic anaemia or cutaneous symptoms [1].

We report the third paediatric case of a splenic infarction associated with a transient induction of antiphospholipid (aPL) and/or aPL-binding protein antibodies as a rare complication of acute *M. pneumoniae* infection. To our knowledge, this is the first case of thrombosis following *M. pneumoniae* infection with induction of anti-prothrombin (aPT) antibodies.

2. CLINICAL REPORT:

A previously healthy 12-year-old boy was referred to the University Hospital of Grenoble, France, with suspected pneumonia. He had developed an afebrile cough for 1 month associated with abdominal pain.

On admission, the patient's body temperature was 38°C and the haemodynamic status was stable. Oxygen saturation was 95% under ambient air, with diminished breath sounds over the left hemithorax. The abdominal left upper quadrant was painful, with a clinical 2-cm splenomegaly. Laboratory test results were

as follows: C-reactive protein, 143 mg/L; white blood cells, 15 g/L; neutrophils, 12 g/L; haemoglobin, 147 g/L; platelets, 359 g/L; lactate dehydrogenase, 554 IU/L ($N < 237$); and lipase, 488 UI/L ($N < 393$). Liver and renal function test results were normal.

A chest X-ray showed left alveolar condensation with mild pleural effusion confirmed by ultrasonography. Abdominal ultrasonography showed a splenic infarction of 95%. Chest and abdominal computerized tomography scan with contrast medium confirmed the splenic infarction due to a total splenic artery thrombosis and revealed bilateral pulmonary condensation with mediastinal adenopathy and left pleural effusion. Cardiac ultrasonography did not show intracardiac thrombus, endocarditis or other emboligenic cardiopathy.

In this context of arterial thrombosis during an infectious process, we performed extended coagulation assays that revealed increased levels of clotting factors of the intrinsic pathway (FVIII > 400%, IX 180%, XI > 200%), of Willebrand factor activity (> 200%) and antigen (> 420%), and of fibrinogen (5.9g/l), most likely due to inflammation. FII, FV and FX values were normal, at 109%, 115% and 121%, respectively. The prothrombin time and activated partial thromboplastin time ratio were normal at 76% and 0.96, respectively. Thrombophilia screening showed positivity for aPT IgM and IgG antibodies at 142 U and 26.3 U, respectively (reference value <18) (ELISA, Theradiag) and the presence of cold agglutinins. The quantification of aPT antibodies can be performed by homemade or commercial enzyme-linked immunosorbent assay (ELISA) [2]. Test results for anti-cardiolipin (aCL) antibodies and anti-beta2glycoprotein I (a β 2GPI) antibodies were negative (chemiluminescent immunoassay, Werfen). Testing for lupus anticoagulant was negative (the two conventional screening tests [i.e., dilute Russell's viper venom time and sensitive aPTT with low phospholipid and silica as activator] yielded negative results). Levels of antithrombin, protein S, protein C, and homocysteine were normal. The factor V Leiden mutation and the prothrombin G20210A gene mutation were absent. Complement test results showed an inflammatory profile with elevated levels of C4 and C3 (388 mg/L and 1880 mg/L, respectively) as well as increased haemolysis by the classical complement pathway (CH50) (154%). Haemoglobin electrophoresis results were normal. Haemopathy was excluded with a normal myelogram. Acute *M. pneumoniae* infection was confirmed by ELISA with positive IgM (3.6 UA/mL for a normal value < 1 UA/mL) and negative IgG (5 UA/ml for a normal value < 10 UA/mL). Extensive serology testing ruled out other viral or bacterial infections: HIV,

hepatitis B and C, parvovirus B19, CMV, EBV, tuberculosis, rickettsiosis, *Coxiella burnetii*, *Bartonella henselae*, borreliosis, toxoplasmosis. Blood cultures remained negative.

The patient was treated with azithromycin for 5 days, which led to a rapid resolution of the pulmonary symptoms. He also received heparin for the first 10 days followed by a 3-month course of vitamin K antagonist. Three months later, aPL and aPT antibodies were negative, and ultrasonography showed normal spleen vascularization without thrombosis. A chest X-ray was normal.

3. DISCUSSION:

Splenic infarction is an uncommon diagnosis and only a few case series have been reported to date. In the study of Schattner et al., the most common factor associated with splenic infarction was emboligenic cardiopathy (62.5%), followed by auto-immune disease such as antiphospholipid syndrome (APS) and lupus (12.5%), infections (septicaemia, VZV, 12.5%), and haematological malignancy (6%) [3].

To our knowledge, there is no large paediatric study on splenic thrombosis. Two cases of children with splenic infarction following *M. pneumoniae* infection have been previously described. Both cases had transient positive aPL antibodies (aCL antibodies, a β 2GPI antibodies and LA) and a left pleuropneumonia [4].

Mycoplasma pneumoniae is a cause of upper or lower respiratory infections. The most common extra-pulmonary complications involve the central nervous system (encephalitis and Guillain–Barré syndrome). Other manifestations are cutaneous symptoms, myalgias, arthralgias and cardiac complications (pericarditis, myocarditis). Haemolytic anaemia is a rare but typical complication.

Several mechanisms have been proposed for extra-pulmonary manifestations [1]:

- Direct invasion;
- Cytotoxicity and inflammation through the activation of immune system cells for cytokine production;
- Immune response with the production of cross-reactive antibodies by molecular mimicry, which may trigger auto-immune disorders. It is probably the mechanism for extrapulmonary manifestations like Guillain–Barré syndrome (resulting from autoantibody-mediated destruction of peripheral nerve fibres), or haemolytic anaemia (due to cross-reacting antibodies against erythrocyte antigens).

In the present case, extrapulmonary manifestation of *M. pneumoniae* pneumonia was splenic infarction associated with transient aPT antibodies. The negativity of aPL after 3 months did not confirm the diagnosis of APS. Furthermore, aPT antibodies are not part of the Sydney classification for a definite APS. APS is defined by the presence of persistent aPL with clinical thromboembolic manifestations or obstetric morbidity. The updated classification criteria are as follows: at least one clinical criterion and one biological criterion among the triad: LA, aCL antibody or a β 2GPI antibody present at least 12 weeks apart [5]. However, some experts suggested the potential of aPT antibody detection in better identification of APS [6], but the specificity of these antibodies for a diagnosis of APS would be low [5].

Apart from APS, many viral or bacterial infections have been described to be associated with the presence of aPL antibodies that seems to result from an auto-immune reaction by molecular mimicry. These infection-induced aPL were considered as transient and non-pathogenic. However, recent studies report cases of thromboembolic manifestations following infection with aPL antibodies [7]. In a systematic review of case reports published in 2016, 293 cases of patients who developed aPL antibodies following infections were described [8]. Three groups were identified and compared: one group of patients fulfilling APS criteria, a second group with transient aPL with thromboembolic events, and a third group with aPL without thromboembolic events. In total, 14 of 293 (4.8%) cases of *M. pneumoniae* infections were reported (one in the APS group, 11 in the group with transient aPL and thrombotic complications, and two in the last group).

In the literature, nine paediatric cases of thrombosis associated with *M. pneumoniae* infection have been reported with aPL development [4,9,10]. Table 1 lists the characteristics of these patients. aPL antibodies were those of the classic APS triad: aCL, a β 2GPI and LA. In our case, only aPT antibodies were positive. Testing for LA, a β 2GPI and aCL yielded negative results.

aPT antibodies detected by ELISA are a heterogeneous population including antibodies against prothrombin alone and antibodies directed against the phosphatidylserine/prothrombin complex (aPS/PT) [5]. Data on the clinical association between aPT alone and clinical manifestations are controversial. Nevertheless, several cohort studies suggest a pathogenicity of aPT antibodies with thromboembolic manifestations. In 2004, a report was published of a cohort of 236 patients with aPT antibodies positivity that was significantly associated with the prevalence of prior thromboembolism [11]. The possible mechanisms by which aPT

could play a role in thrombosis formation are: aPT-mediated activation of platelets, direct effect on endothelium by inhibition of prothrombin-mediated endothelial cell prostacyclin release, inhibition of protein C activation, and activation of endothelial cells by recognizing the prothrombin anionic phospholipid complex and inducing procoagulant substances.

On the other hand, some studies have demonstrated that antibodies directed against the phosphatidylserine/prothrombin complex (aPS/PT) are associated with thrombosis and the obstetric complications of APS (12,13). In a recent study, Tonello et al. reported that IgG aPS/PT antibodies could be included in the list of risk factors predictive of a first thrombotic event in aPL carriers [12].

We postulate that acute *M. pneumoniae* infection resulted in the transient development of aPT antibodies, which might have contributed to a hypercoagulability state and to thrombosis formation in the splenic artery. Nevertheless, the occurrence of this thrombosis may have been multifactorial. We cannot rule out that local inflammation due to left-sided pneumonia and pleural effusion may have promoted thrombosis of the splenic artery. In addition, cold agglutinin, even without activation of haemolysis, could have played a role.

The two cases of children with splenic infarction following *M. pneumoniae* infection described by Witmer et al. had similar characteristics [4]. Both cases had a transient elevation of aPL antibodies and presented with left pleuropneumonia, corroborating both hypotheses (global hypercoagulability and local inflammation). But the aPL antibodies profile was still different with the positivity of LA, $\alpha\beta 2\text{GP1}$ and aCL, which are well known to be able to induce thrombosis in APS. To our knowledge, we report here the first case of thrombosis following *M. pneumoniae* infection with high-titre aPT positivity. It raises the question of the pathogenicity of these antibodies in the occurrence of thrombosis in this context.

It should be noted, however, that a number of cases of thrombosis following *Mycoplasma* infection have been described without aPL antibodies [4]. But all previously reported cases were not tested for all aPL antibodies and for aPT. An exhaustive search for aPL and aPT antibodies could be interesting in the cases of thrombosis complicating *M. pneumoniae* infection.

This report has a limitation regarding the diagnosis of *M. pneumoniae* infection. Even if the clinical presentation was highly compatible with this diagnosis, only a single serology test for *M. pneumoniae* was performed. A second serology test might have helped to confirm our hypothesis. Moreover, some authors question the diagnostic value of *M. pneumoniae* serology, which is also positive in asymptomatic carriers

[14]. In our case, we considered that the clinical picture and the favourable evolution of pneumonia under antibiotic therapy were in favour of an actual *Mycoplasma pneumoniae* infection.

4. Conclusion

Mycoplasma pneumoniae pneumonia is a common infection in paediatrics. As in other infections, aPL can develop in this context, most often with no thromboembolic manifestation. Children who have an atypical evolution with abnormal pain or persistence of fever despite adequate treatment should be monitored and examined to search for abdominal thrombosis. In the case of thrombosis, a thorough thrombophilia test should be performed with a search for aPL antibodies.

Considering the scarcity of thrombotic complications in *M. pneumoniae* infections, we suggest that aPL antibody screening should not be restricted to aCL and a β 2GPI antibodies, but may also include aPT and aPS/PT, even if these antibodies are not part of currently applied criteria for APS and despite their controversial role in the aetiology of thrombosis. Further studies are needed to confirm the thrombopathogenicity of aPT.

Conflicts of interest: none

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ABBREVIATIONS:

a β 2GPI: anti-beta2-glycoprotein I

aCL: anti-cardiolipin

aPL: antiphospholipid

APS: antiphospholipid syndrome

aPS/PT: anti-phosphatidylserine/prothrombin

aPT: anti-prothrombin

ELISA: enzyme-linked immunosorbent assay

IgG: immunoglobulin G

IgM: immunoglobulin M

LA: lupus anticoagulant

Table 1: Review of the literature: *Mycoplasma pneumoniae* infections in paediatrics complicated with thrombosis and antiphospholipid antibodies

References	Age (years), sex	Time since the first symptoms	Localization of infection	Thrombosis localization	Antiphospholipid antibodies	Time to negative antibodies	Cold agglutinin
Our case	12, M	1 month	Left lower lobe pneumonia with pleural effusion	Splenic infarction	- aPT IgM and IgG	- 3 months	NA
Nagashima M, et al. (4)	13, F	>12 days	Left lower lobe pneumonia with pleural effusion	Splenic infarction	- LA - aCL IgM - aB2GPI IgM	- 1 year - moderate positive 5 weeks - 5 weeks	positive
Nagashima M, et al. (4)	10, M	>15 days	Left lower lobe pneumonia with pleural effusion	Splenic infarction	- LA - aCL IgM - aB2GPI IgM	- 5 weeks	NA
Nagashima M, et al. (4)	9, M	8 days	Pneumonia	Cardiac thrombus (Right ventricle)	- aCL IgM	- 6 months	positive
Nagashima M, et al. (4)	11, M	10 days	Right lower lobe pneumonia with pleural effusion	Pulmonary embolism (Right pulmonary artery)	- LA - ANA	- NA	NA
Nagashima M, et al. (4)	13, M	2 weeks	Left lower lobe pneumonia with pleural effusion	Pulmonary embolism (Right pulmonary artery) Left popliteal vein thrombosis	- LA - aCL IgM and IgG But protein S deficiency discovered in the same time	- 5 months	positive
Nagashima M, et al. (4)	6, M	3 weeks	Left lower lobe pneumonia with pleural effusion	Ileo-femoral thrombosis Pulmonary embolism (Right pulmonary artery)	- aCL IgM and IgG - LA - Acquired activated protein C resistance	- Few weeks	positive
Nagashima M, et al. (4)	4, M	No delay	Left lower lobe pneumonia with pleural effusion Encephalopathy	Cardiac thrombus (Left atrial)	- Undefined aPL IgM	- 6 months	positive
Su H, et al. (data from abstract only) (9)	6, M	15 days	Left lower lobe pneumonia with pleural effusion	Pulmonary embolism (Left lower bronchial artery)	- aCL	- 3 months	positive
Tanir G, et al.(10)	7, F	10 days	Left lower lobe pneumonia with atelectasis	Left internal carotid artery thrombosis	- aCL IgM	NA	negative

M: male, *F*: Female, *NA*: not available, *LA*: lupus anticoagulant, *aCL*: anticardiolipin, *aB2GPI*: antiB2-glycoprotein I, *aPL*: antiphospholipid, *ANA*: antinuclear antibody, *IgG*: immunoglobulin G, *IgM*: immunoglobulin M.