Thrombosis associated with *mycoplasma pneumoniae* infection (Review)

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Abstract. *Mycoplasma pneumoniae* is a common pathogen causing respiratory infections in children and adults. In addition to respiratory diseases, *Mycoplasma pneumoniae* is also involved in numerous extrapulmonary diseases. Thrombosis is an extrapulmonary manifestation associated with *Mycoplasma pneumoniae* infection. In recent years, an increasing number of case reports have been published identifying thrombosis secondary to *Mycoplasma pneumoniae* infection. In the present study, the available relevant literature in English available on PubMed, Medline and Web of Science was consulted. The results of the present study demonstrated that in patients with thrombosis caused by *Mycoplasma pneumoniae* infection, some of the factors causing thrombosis are transient and some are due to hereditary thrombophilia. Following timely treatment, the majority of patients recovered completely but some patients had a poor prognosis. The present review focuses on the pathogenesis, clinical features, treatment and prognosis of this crucial issue, which contributes toward the understanding of the disease.

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1. Introduction

Mycoplasma pneumoniae is the smallest self-replicating organism in terms of genome length and cellular size (1). Mycoplasma pneumonia occurs worldwide throughout the year, but it is more common in the summer or early autumn (2) and may be spread from person to person through aerosols (3). These infections can be detected by culture, serology and molecular-based assays. Serum antibody detection is the most frequently used method for retrospective diagnosis of *Mycoplasma pneumoniae* infection (4). Possible mechanisms of damage to host cell by mycoplasma pneumonia is through competition for precursors, adherence to cells, fusion to the cell and cytopathic effects (5).

Respiratory infection is a common disease, which can be caused by *Staphylococcus aureus* (6,7), *Mycoplasma pneumoniae* and other pathogens. Tracheobronchitis is another very common clinical manifestation induced by *Mycoplasma pneumoniae* infection; however, pneumonia is the most important clinical illness associated with *Mycoplasma pneumoniae* infections (2). It is well known that *Mycoplasma pneumoniae* is a common cause of community-acquired pneumonia in children and adults (8). In endemic periods, 4-8% of all cases of community-acquired pneumonia were attributed to *Mycoplasma pneumoniae* and during incidence peaks, up to 40% of community-acquired pneumonia cases were from *Mycoplasma pneumonia* (9). *Mycoplasma pneumoniae* infection is generally self-limiting and mild; however, in some patients it may develop into a severe or life-threatening disease (10). There are also many asymptomatic children who carry *Mycoplasma pneumoniae* in their upper respiratory tract and it may persist in the respiratory tract for weeks or even months after infection (11).

Aside from respiratory diseases, *Mycoplasma pneumoniae* is also involved in the development of some extra-respiratory diseases (12). Previous studies have reported that *Mycoplasma pneumoniae* is involved in extra-respiratory diseases of the skin, musculoskeletal (13,14), cardiovascular (15,16), hematological (17,18), gastro-intestinal (19,20), neurological (21,22) and renal (23) systems. These conditions may have variable clinical features

and may appear in immunologically predisposed children with recurrent or persistent *Mycoplasma pneumoniae* infection (24). *Mycoplasma pneumoniae* can involve almost any part of the body and can develop into extensive extrapulmonary manifestations (12). A retrospective study of children with *Mycoplasma pneumoniae* infection demonstrated that delayed effective treatment was associated with extrapulmonary manifestations (25). A prospective study revealed that the serum immunoglobulin E level in children with *Mycoplasma pneumoniae*-related extrapulmonary diseases was significantly higher compared with in children with only *Mycoplasma pneumoniae*-related respiratory illnesses (26). Certain individuals, who are prone to produce immunoglobulin E, may be predisposed to develop extra-respiratory diseases associated with *Mycoplasma pneumoniae* acute infections (27).

Thrombosis is one of the extra-respiratory manifestations associated with *Mycoplasma pneumoniae* infection (12). With an improved understanding of *Mycoplasma pneumoniae*, case reports of thrombosis associated with *Mycoplasma pneumoniae* infection are increasing (28-61). Thrombosis is a major cause of mortality and disability worldwide (62). Arterial thrombosis is usually associated with plaque rupture, which triggers platelets to develop platelet rich clots; however, venous thromboembolism is associated with endothelial dysfunction and blood stasis, leading to fibrin- and erythrocyte-rich thrombus (62). Following *Mycoplasma pneumoniae* infection, thrombosis may occur in a different part of the body, sometimes affecting the prognosis of the disease (29,30). The present review summarizes the pathogenesis, clinical features, treatment and prognosis of thrombosis induced by *Mycoplasma pneumoniae* infection in order to better understand this complication.

2. Methods

Comprehensive searches of PubMed, Medline, and Web of Science were performed to identify all published reports on patients with thrombosis associated with *Mycoplasma pneumoniae* infection. Search terms included: '*Mycoplasma pneumoniae*' and 'thrombus' or 'embolism' or 'thrombosis' or 'thrombotic' or 'thromboembolism'. Results published between January 1970 and December 2020 were included. Only full-text, English-language papers were included. Duplicate publications and irrelevant topics were excluded. Data collected included the location of thrombosis, thrombosis onset time since *Mycoplasma pneumoniae* infection, laboratory examination regarding thrombosis, and pathogenesis of thrombosis.

3. Location of thrombosis

Patients with *Mycoplasma pneumoniae* infection may present with thrombus in almost any part of the body (Tables I-VI) Thrombosis caused by *Mycoplasma pneumoniae* infection was most reported in the head and neck, followed by in the limbs. Certain patients with normal chest radiography and *Mycoplasma pneumoniae* infection also developed thrombi (28,33,34). Certain patients developed thrombi in only one part of the body, while others developed thrombi in multiple parts. One patient developed an aortic thrombus, a right peroneal artery embolus, a splenic infarct and a renal infarct (28).

4. Thrombosis onset time from *Mycoplasma pneumoniae* infection

Cerebral infarction developed 2 days to 3 weeks after *Mycoplasma pneumoniae* infection (29-31,33-41,43,44). Chest imaging of certain patients revealed pulmonary embolism 11-29 days after *Mycoplasma pneumonia* infection (52). A previous case report identified a cardiac thrombus 4 days after *Mycoplasma pneumoniae* infection (46). Thrombi in abdominal organs developed ~1 week to 1 month after *Mycoplasma pneumoniae* infection (28,48-51). Thrombosis in the extremities appeared ~1-2 weeks after *Mycoplasma pneumoniae* infection (28,41,53-57) while thrombotic microangiopathy occurred 3 days to 3 weeks after infection (58,59,61).

5. Laboratory examination for thrombosis

Children with *Mycoplasma pneumoniae* pneumonia had higher plasma fibrinogen and D dimer levels than healthy children (63). They also had shorter prothrombin and activated partial thromboplastin times (63). The increased fibrinogen and D-dimer levels may induce a hypercoagulable state, which appears 6-15 days after *Mycoplasma pneumoniae* pneumonia onset (32). Extensive coagulation studies were performed, including plasma levels of clotting factors, proteins C and S, plasminogen, antithrombin III, lupus anticoagulant, sickle cell anemia, homocysteine antiphospholipid syndrome, disorders of fibrinolysis, anticardiolipin antibody and cold agglutinins (30,39,43,48). Tests for inherited thrombophilia are controversial and certain studies have suggested that these tests for inherited thrombophilia should never be performed (64). Inherited thrombophilia is usually identified by a coagulation specialist based on their personal and family history of venous thromboembolism, but a diagnosis can be made without the results of these tests (64).

6. Pathogenesis of thrombosis

Mycoplasma pneumonia may directly cause local thrombosis occlusion by affecting the vascular wall without systemic hypercoagulability (65). An autopsy of a patient with acute myocardial infarction revealed that *Mycoplasma pneumoniae* was present in the unstable segments of the intima (66). Furthermore, *Mycoplasma pneumoniae* is frequently found in atherosclerotic plaques (67). In addition, systemic hypercoagulability through the activation of chemical mediators, including complement, may result in thrombotic vessel occlusion (65).

Familial thrombophilia. Some of the included patients were diagnosed with familial thrombophilia and *Mycoplasma pneumoniae* infection. A man with *Mycoplasma pneumoniae* infection developed thrombi due to a homozygous methylenetetrahydrofolate mutation, increased homocysteine concentration and decreased folic acid level (33). Another boy with a heterozygous methylenetetrahydrofolate

Table I. Summary of thrombosis cases in the brain and neck associated with *Mycoplasma pneumoniae* infection.

No.	Pulmonary infection	Thrombus or infarction site	(Refs.)
1	Yes	Right middle cerebral artery	(29)
2	Yes	Right vertebral and basilar arteries	(30)
3	Yes	Right lenticulostriate artery	(31)
4	Yes	Right middle cerebral artery	(35)
5	Yes	Left middle cerebral artery	(36)
6	Yes	Deep cerebral and dural venous sinus	(37)
7	Yes	Left carotid artery	(38)
8	No	Left centrum semiovale	(34)
9	No	Right vertebral and midbasilar arteries	(33)
10	Yes	Left posterior cerebral artery	(39)
11	Yes	Left internal carotid artery and the middle cerebral artery	(40)
12	Yes	Left middle cerebral artery	(41)
13	Yes	Right anterior cerebral artery/middle cerebral artery and left middle cerebral artery	(42)
14	Yes	Acute infarctions of both posterior cerebral arteries and left middle cerebral artery territories	(43)
15	Yes	Left middle cerebral artery	(44)
16	Unknown	Cerebrovascular infarction	(45)

Table II. Summary of thrombosis cases in the heart and aorta associated with *Mycoplasma pneumoniae* infection.

No.	Respiratory infection	Thrombus site	(Refs.)
1	Yes	Right ventricle	(46)
2	Yes	Left ventricle	(47)
3	Yes	Tricuspid valve chordae tendineae, under the tricuspid valve, and left atrium	(32)
4	No	Aorta	(28)

Table III. Summary of thrombosis cases in the abdomen associated with *Mycoplasma pneumoniae* infection.

No.	Respiratory infection	Thrombus site	(Refs.)
1	Yes	Splenic	(48)
2	No	Splenic	(49)
3	No	Splenic	(50)
4	Yes	Splenic	(51)
5	Yes	Splenic	(51)
6	No	Renal and splenic	(28)
7	Yes	Splenic artery, celiac trunk artery, and superior mesenteric artery	(32)

mutation also developed cerebral infarction following *Mycoplasma pneumoniae* infection, but his homocysteine concentration remained normal (30). Methylenetetrahydrofolate enzyme dysfunction may cause hyperhomocysteinemia (68). Patients with increased homocysteine levels are prone to develop thrombi (69). Hyperhomocysteinemia may lead to endothelial dysfunction, by suppressing nitric oxide production and endothelial nitric oxide synthase activity (70). However, another study demonstrated that hyperhomocysteinemia did not increase the risk of developing venous thrombus following adjusting for confounding factors (71). One case described a girl with thrombosis secondary to *Mycoplasma pneumoniae* pneumonia who was diagnosed with familial antithrombin III deficiency (56). Antithrombin is a natural anticoagulant which suppresses active clotting factors particularly thrombin and activated factor X (72,73). Patients with antithrombin deficiency have a significantly increased risk of thromboembolism, particularly in the venous circulation (74).

Table IV. Summary of thrombosis cases in the lung associated with *Mycoplasma pneumoniae* infection.

No.	Respiratory infection	Thrombus site	(Refs.)
1	Yes	Lung	(52)
2	Yes	Left lung	(53)
3	Yes	Right lung	(54)
4	Yes	Lung (including pulmonary artery and vein)	(32)

Table V. Summary of thrombosis cases in the limbs associated with *Mycoplasma pneumoniae* infection.

No.	Pulmonary infection	Thrombus site	(Refs.)
1	Yes	Right popliteal artery and its distal branches	(55)
2	Yes	Fibular vein, posterior tibial vein, and femoral vein	(53)
3	Yes	Left popliteal vein	(54)
4	Yes	Left femoral vein	(56)
5	Unknown	Left-sided popliteal vein, femoral vein, external and internal iliac veins, and common iliac vein	(57)
6	No	Right peroneal artery	(28)
7	Yes	Both femoral veins	(41)
8	Yes	Popliteal artery, posterior tibial artery, external iliac vein, common iliac vein, common femoral vein, great saphenous vein, internal iliac vein cephalic vein, and superficial vein of cubital fossa	(32)

Table VI. Summary of thrombotic microangiopathy cases associated with *Mycoplasma pneumoniae* infection.

No.	Respiratory infection	Thrombotic microangiopathy	(Refs.)
1	Yes	Thrombotic thrombocytopenic purpura	(58)
2	Yes	Hemolytic uremic syndrome	(59)
3	Unknown	Thrombotic thrombocytopenic purpura	(60)
4	Yes	Thrombotic thrombocytopenic purpura	(61)

Antiphospholipid antibodies. Certain studies and case reports have demonstrated that patients with thrombosis secondary to *Mycoplasma pneumoniae* infection were positive for anticardiolipin antibodies, β2-glycoprotein antibodies or lupus anticoagulant antibodies (28,32,46,51,53,54). These aforementioned antibodies were transient and became negative in certain patients 3-6 months after initial disease onset (28,32,46,53,54). Anticardiolipin antibody, β2-glycoprotein antibody and lupus anticoagulant antibody are all antiphospholipid antibodies, which reacts to phospholipids, phospholipid-protein complexes and phospholipid-binding proteins (75,76). The antiphospholipid antibodies contribute toward the formation of a thrombus (76). Antiphospholipid antibodies cause thrombosis through protein phosphatase 2A activation via apolipoprotein E receptor 2, disabled-2 and src homology domain-containing transforming protein 1 complex formation in the endothelium (77). Patients with thrombosis and positive antiphospholipid antibodies are also likely to develop thrombosis again (78).

Anti-prothrombin antibodies. Certain patients with thrombosis associated with *Mycoplasma pneumoniae* infection were positive for anti-prothrombin antibodies, which was resolved 3 months after the acute illness (48,54). Anti-prothrombin antibody is not a criterion for diagnosing anti-phospholipid syndrome and is referred to as noncriteria antibody (79). Anti-prothrombin antibody increases the risk of thrombosis (80,81).

Increased coagulation factors. Certain patients with thrombosis secondary to *Mycoplasma pneumoniae* infection had increased factor VIII (28). However, this phenomenon was transient, and the factor VIII levels were normal 3 months after the acute disease (28). Certain patients with thrombosis induced by *Mycoplasma pneumoniae* infection had increased von Willebrand factor activity and increased levels of intrinsic pathway clotting factors, including factor VIII, factor IX and factor XI (48). These increased coagulation factors contribute toward the formation of thrombosis.

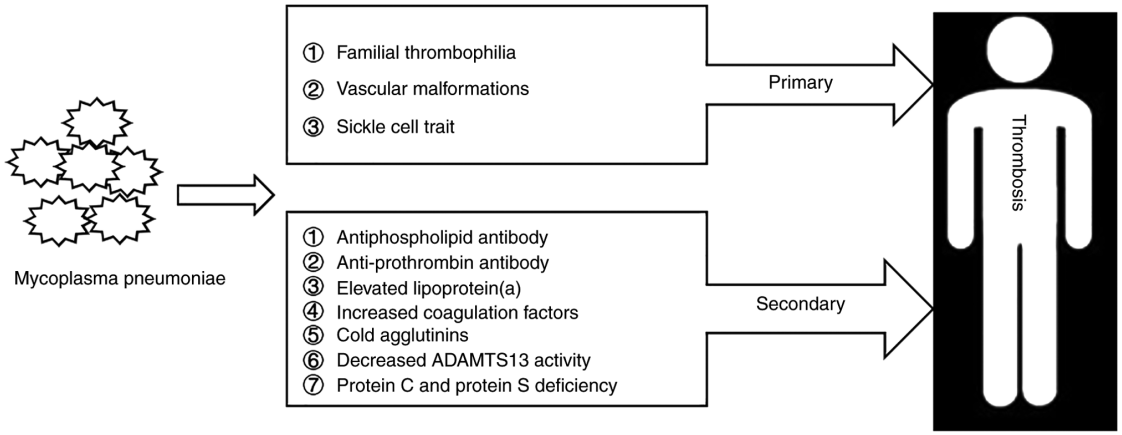

Figure 1. Patients with *Mycoplasma pneumoniae* infection may develop thrombi in any part of the body, which is due to primary and secondary factors.

Cold agglutinins. Cold agglutinins were present in certain patients with thrombosis induced by *Mycoplasma pneumoniae* infection (46,48). Cold agglutinins induce hemolysis and anemia by binding to the erythrocyte antigen at a lower temperature and triggering the classical complement pathway (82). Hemolysis may contribute toward thrombosis by increasing circulating procoagulant microparticles (83), hyperactivating hemoglobin-bound von Willebrand factor multimers (84) and promoting platelet aggregation (85).

Lipoprotein (a). Certain patients with thrombosis induced by *Mycoplasma pneumoniae* infection had increased lipoprotein (a) (51). Lipoprotein contributes toward thrombotic disorder (86). Patients with higher levels of lipoprotein (a) had impaired fibrinolysis (86), which may be induced by interfering with the binding of plasminogen to fibrin (87), inhibiting plasminogen activation (88), and decreasing the generation of plasmin (89).

Vascular malformations. A boy without an inferior vena cava developed deep venous thrombosis and *Mycoplasma pneumoniae* infection (57). Certain vascular malformations, including the absence of the inferior vena cava contribute toward the development of thrombosis (90). There have also been other reports of thrombosis associated with vascular malformations (91-93). Vascular malformations are complex congenital diseases, which occur due to abnormalities during the process of vasculogenesis (94). Certain vascular malformations are characterized by slow-flow (94). Slow deep venous flow in the lower extremities correlates with an increased rate of subsequent deep venous thrombosis (95). Slow-flow of vascular malformations serves a role in the process of thrombosis associated with *Mycoplasma pneumoniae* infection. A previous study supported the role of *Mycoplasma pneumoniae* in the formation of aneurysms (96). A patient with *Mycoplasma pneumoniae* infection presented with aortic and subclavian aneurysm and acute cerebral infarction (34). There is a significant risk of thrombosis in patients with an aneurysm (97).

Sickle cell trait. One case report described a boy with *Mycoplasma pneumoniae* infection who developed a posterior cerebral artery occlusion; he also had the sickle cell trait and a normal thrombophilia examination (39). Previous case reports have described patients with the sickle cell trait who formed a thrombus (98-100). Sickle cell trait is a heterozygous form of sickle cell anemia (101). Patient with sickle cell trait have slightly decreased erythrocyte deformability, increased erythrocyte aggregation (102) and increased blood viscosity (101,103,104). These characteristics may serve an important role in the development of thrombosis associated with *Mycoplasma pneumoniae* infection.

ADAMTS13 enzyme. *Mycoplasma pneumoniae* infection may affect the activity of the ADAMTS13 enzyme. A woman with thrombotic microangiopathy associated with *Mycoplasma pneumonia* infection had high anti-ADAMTS13 antibodies at the beginning of infection and her plasma ADAMTS13 enzyme activity was normal 1 month after clinical resolution (58). Another patient with hemolytic uremic syndrome complicated by *Mycoplasma pneumoniae* infection presented with a moderate decrease in ADAMTS13 activity following admission, but it increased to the normal levels during follow-up (59). The protease ADAMTS-13 may cleave the von Willebrand factor and decrease its thrombogenicity (105). Acquired deficiency of ADAMTS-13 is secondary to sepsis (106). Deficiency of ADAMTS-13 may cause thrombotic microangiopathy (107). Inflammation may affect ADAMTS13 activity by oxidative modification (108). During inflammation, interleukin-6 partially suppresses ADAMTS13 activity (109), while interleukin-8 and tumor necrosis factor increase the release of the von Willebrand factor, which exceeds the processing capacity of ADAMTS13 and leads to thrombosis (109).

Protein C and protein S. Acute hepatitis is an extrapulmonary disease induced by *Mycoplasma pneumonia* (1). Abnormal liver function is not infrequently seen in patients with *Mycoplasma pneumoniae* infection (1) as proteins C and S are predominantly produced by hepatocytes. Activated protein C inhibits thrombosis by deactivating activated factors V and VIII. Protein S serves as a co-factor during this process (110-112). Patients with hepatic cirrhosis usually have low levels of protein C and high levels of factor VIII. This

increased factor VIII/protein C ratio contributes toward the development of a thrombophilia state (113). The insufficiency of protein C destroys the balance between procoagulant and anticoagulant proteins; therefore, individuals are prone to develop thromboembolism (111). Abnormal liver function may affect the synthesis of protein C and protein S in patients with *Mycoplasma pneumoniae* infection, thereby predisposing them to thrombosis. There were several reported cases of thrombosis and *Mycoplasma pneumoniae* infection, which reported low levels of protein S (30-32,54). One month after the initial disease, the level of protein S had increased to the normal range (31), while another study reported that the protein S activity became normal after 6 months (32).

7. Treatment of thrombosis

In addition to treatment with antibiotics, patients underwent various methods to treat thrombosis associated with *Mycoplasma pneumoniae* infection. In cases where the thrombus partially detached and was almost floating in the right ventricle, it was removed by cardiac surgery (46). Due to shape change and size reduction of the thrombus, another patient with left ventricular thrombus and *Mycoplasma pneumoniae* infection also underwent urgent surgery (47). In another case, an extremity deep vein thrombosis in a man with mycoplasma pneumonia was not absorbed despite strong anticoagulant therapy, and therefore a filter was implanted into his inferior vena cava to prevent the thromboembolism recurring (41). Another boy with posterior cerebral artery occlusion secondary to *Mycoplasma pneumoniae* infection was treated with a low dose of aspirin (39). In other cases, thrombolytic therapy with urokinase was performed in severe clinical condition (37,55).

8. Prognosis of thrombosis

Following anticoagulant treatment, the thrombus absorption time of the majority of patients was more than 3 months, but was 1.5 to 3 months in some others. However, in the majority of patients, thrombus-related symptoms disappeared within 1 month (32). However, certain patients may also have sequelae, particularly patients with cerebral thrombi. In one case, a boy with *Mycoplasma pneumoniae* pneumonia and cerebral infarction still had poor right hand grip power at the 6-month follow-up visit (40). In another case, an adult with *Mycoplasma pneumoniae* pneumonia and cerebral infarction slowly recovered from hemiplegia but continued to have a residual deficit (29). Certain case reports with cerebral infarction secondary to *Mycoplasma pneumoniae* pneumonia reported that patients' neurological symptoms completely resolved (31,34,41).

9. Prevention of thrombosis

The risk factors of thrombosis in patients with *Mycoplasma pneumoniae* infection should be identified. Pulmonary consolidation and high levels of inflammatory markers were found to be risk factors for patients with severe *Mycoplasma pneumoniae* pneumonia to develop thrombus (32). Predisposing factors associated with a hypercoagulable state also contribute toward thrombosis. One study suggested that clinicians should weigh the risks and benefits of low molecular weight heparin prophylaxis in patients with mycoplasma infection at risk for thrombosis (114).

10. Limitations

In-depth studies into the mechanism of how *Mycoplasma pneumoniae* infection causes thrombosis have not been published; therefore, the summary of the mechanism in this review may be too superficial.

11. Conclusions

Further attention should be paid to the extrapulmonary manifestations associated with *Mycoplasma pneumoniae* infection, particularly thrombosis. The mechanism of thrombosis in patients with *Mycoplasma pneumoniae* infection includes numerous factors, and thrombi induced by *Mycoplasma pneumoniae* infection may occur in any part of the body (Fig. 1). Early diagnosis and timely therapy may improve the prognosis of these patients.

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YL designed the study. JL wrote the manuscript. Data authentication is not applicable for this study. Both authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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