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Venous thromboembolism during mycoplasma pneumoniae infection: case report and review of the literature

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Abstract. – Mycoplasma pneumoniae infection is frequent but generally mild or self-limiting. Approximately 10% of cases develop clinical signs of pneumonia with "atypical" radiographic pattern. However, mycoplasma pneumoniae can be responsible for a variety of extrapulmonary manifestations, potentially involving all systems and apparatuses. Although exact pathophysiological mechanisms are not completely known, these could be secondary to direct invasion of the target organ, immunological damage due to molecular mimicry or vascular obstruction.

A 45-year-old man was admitted to Internal Medicine Unit because of fever, dry cough and fatigue lasting 15 days. Fever disappeared after starting clarithromycin. About 72 h after admission the patient complained of right calf pain and tachypnea. The presence of anti-mycoplasma antibodies suggested mycoplasma pneumoniae infection. Moreover, a diagnosis of venous thrombo-embolism was performed. Given the absence of classical risk factors for thrombosis, patient was investigated for inherited and acquired thrombophilia and tested positive for antiphospholipid antibodies.

A review of the English literature on the association between m. pneumoniae and pulmonary embolism will be provided in order to underline the possible pathogenetic role of antiphospholipid antibodies in this setting. Clinicians should outweigh risk and benefits for LMWH prophylaxis case by case considering these adjunctive pro-thrombotic mechanisms in patients m. pneumoniae infection.

Key Words:
Atypical pneumonia, Pulmonary embolism, Deep Atypical pneumonia, Pulmonary embolism, Deep vein thrombosis, Lupus anticoagulant, Antiphospholipid antibodies.

Introduction

Mycoplasma species represent the smallest, in terms of dimensions and genome size, self-replicating and free-living organisms[1]. The term *mycoplasma* (in Greek: "*mykes*", fungus, and "*plasma*", formed) refers to a group of pleomorphic microorganisms lacking of a rigid cell wall. These structural features confer them both advantages, in terms of plasticity and resistance to common antibiotics, and disadvantages, such as the need for a host cell for replication[2].

First described by Eaton et al[3], mycoplasma pneumoniae (MP) represents a frequent cause of disease in humans[4]. The infection is generally mild or self-limiting; however, about 10% of infected patients develop pneumonia, with a radiographic pattern of atypical pneumonia[5]. In addition to respiratory manifestations involving upper and lower respiratory tract, about 25% of MP cases are characterized by extrapulmonary manifestations. These can occur before, during, or after pulmonary symptoms, or even in the absence of respiratory illness[6]. Extrapulmonary manifestations can affect almost all systems as summarized in Table I. Their pathophysiological mechanisms are not completely understood, although several hypotheses have been formulated, such as direct organ invasion, activation of immune system resulting in cytotoxicity and inflammation, autoimmunity with production of autoantibodies due molecular mimicry[7,8].

Venous thromboembolism (VTE) represents a possible complication of acutely ill medical

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Table I. Extrapulmonary manifestations of mycoplasma pneumoniae infection.

System involved	Pathogenetic mechanism			
	Vascular thrombosis	Direct type	Indirect type	Unknown
Cardiovascular	Cardiac thrombosis, venous/arterial thrombosis, Pulmonary embolism	Endocarditis, Pericarditis	Myocarditis/ Kawasaki disease	
Mucocutaneous			Erythema multiforme, erythema nodosum, Stevens-Johnson syndrome, urticaria, anaphylactoid purpura, Henoch-Schonlein purpura, cutaneous vasculitis, mucositis, subcomeal pustular dermatosis.	
Gastrointestinal	Pancreatitis	Early onset hepatitis	Late onset hepatitis	
Hematologic	Disseminated intravascular coagulation, splenic infarct		Autoimmune hemolytic anemia, thrombocytopenic purpura, infectious mononucleosis	
Musculoskeletal		Arthritis	Arthritis, myositis	Rhabdomyolysis
Neurologic	Stoke, psychological disorders, striatal necrosis, thalamic necrosis	Early onset encephalitis, early onset myelitis, aseptic meningitis	Late onset encephalitis /myelitis, Guillain-Barrè syndrome, cranial/ peripheral neuropathies, cerebellitis, acute cerebellar ataxia, opsoclonus-myoclonus syndrome	Acute disseminated encephalomyelitis
Sensor	Sudden hearing loss	Otitis media	Conjunctivitis, iritis, uveitis	
Urogenital	Priapism, renal artery embolism		Glomerulonephritis, IgA nephropathy	

patients[9]. Acute diseases such as pneumonia with respiratory failure significantly raise VTE risk, particularly in patients with pre-existing comorbidities (e.g., obesity, heart failure, elderly, etc.). To reduce this risk, the use of prediction scores to decide the optimal VTE prophylaxis is strongly recommended[10].

Here we describe the occurrence of VTE in a young patient affected by MP infection without pneumonia nor respiratory failure. A review of the literature will be also provided.

Case Presentation

In November 2019, a 45-year-old man was admitted to our Internal Medicine Inpatients Unit because of the persistence for about two weeks of fever (39.5°C peak), dry cough and fatigue. The patient also reported abdominal pain and altered bowel habits (increase of stool frequency). He was working as bricklayer, never smoked. He was not taking any chronic therapies. Past medical history was relevant for glomerulonephritis at the age of 18 years old and for penicillin allergy.

At admission, blood pressure was 120/75 mmHg, heart rate 92 bpm, oxygen saturation 96% room air, respiratory rate 16/minute, body temperature was 38.6°C. Physical examination was normal. Results of laboratory test are shown in Table II. In particular, acute phase reactants (e.g., C-reactive protein, erythrocyte sedimentation rate, procalcitonin), liver enzymes and albumin were altered. Chest X-ray was normal.

Table II. Results of lab tests at admission (T0) and at 3 months (T1) follow-up.

Test	Results – T0	Results – T1	Reference
HB – g/dl	**12.7**	15.5	13-17
WBC – ×1000/uL	6.76	7.45	4.3-10.8
PLT – ×1000/uL	156.00	177.00	130.00-400.00
Sodium (Na) – mmol/L	137.0	140	136.0-145.0
Potassium (K) – mmol/L	3.8	4.2	3.5-5.0
Chloride (Cl) – mmol/L	103.0	107.0	98.0-107.0
Creatinine – mg/dL	1.0	0.80	0.69-1.30
Total protein – g/dL	7.3	7.20	6.40-8.20
Albumin – g/dL	**2.9**	4.50	3.50-5.50
Calcium – mg/dL	9.3	8.80	8.10-10.40
Total bilirubin – mg/dl	1.0	1.00	0.20-1.00
AST – U/L	53	29.00	8.00-30.00
ALT – U/L	**97**	53.00	13.00-57.00
ALK-P – UI/L	**123**	75	45-117
y-GT – UI/L	**189**	47.00	5.00-85.00
PT – %	**68**	24	70-130
INR – ratio	**1.24**	2.58 (on warfarin)	0.80-1.20
PTT – sec	30.5	37.8	20.0-32.0
CRP – mg/dL	17	< 0.290	< 0.290
ESR – mm	75	14.0	2.0-15.0
PCT – ug/L	1.38	0.07	< 0.50
ANA	1:160	Negative	Negative
ENA	Negative	Negative	Negative
aCL IgM – U/mL	**210.8**	13.4	< 15
aCL IgG – U/mL	**70.9**	4.4	< 15
aB2GP1 – U/mL	12.2	3.0	< 20
aB2GP1 IgG – U/mL	5.3	1.6	< 20
LAC	**Positive**	Negative	Negative
aPTT ratio	**1.8**	1.6	< 1.2
dRVVT ratio	**2.2**	2.8	< 1.2
Coombs antibody test – negative	Negative	Negative	Negative
Homocysteinemia – umol/L	6.31	6.46	4.3-11.1
Prothrombin mutation (G20210A)	Absent		Absent
V Leiden factor mutation (G1691A)	Absent		Absent
Cold agglutinins	Absent		

HB = haemoglobin, WBC = white blood count, PLT = Platelet count; AST = Aspartate aminotransferase, ALT = alalnine aminotransferase; ALK-P = alkaline phosphatase, gGT = gamma-glutamyltranspeptidase; PT = Prothrombin time; INR = international normalized ratio; PTT = Partial thromboplastin time; CRP = C reactive protein; ESR = Erythrocyte sedimentation rate; PCT = Procalcitonin; ANA = Antinuclear antibodies; ENA= extractable nuclear antigens; aCL = anti-cardiolipin antibodies; aB2GP1 = anti-beta2-glycoprotein1; LAC = lupus anticoagulant.

Abdominal US-scan showed mild liver steatosis and biliary sludge, no kidneys nor spleen abnormalities, nor ascites. After collection of blood, sputum and urine samples for cultures, empiric treatment with intravenous clarithromycin 500 mg b.i.d. was prescribed. Echocardiography was normal. About 48 h after starting antibiotic, fever disappeared. Microbiological results were consistent with MP infection (anti-MP antibodies titre: 1:320, nv<1:40). About 72 h after admission the patient complained of right calf pain and mild tachypnea (respiratory rate 22 breaths/min with SpO_2 94% room air). D-dimer was high (87730 ng/ml, n.v. <500 ng/ml). Lower limb Doppler US-examination showed deep vein thrombosis of right popliteal, sural and calf veins. Pulmonary CT angiography showed the presence of peripheral pulmonary embolism in segmental and subsegmental branches of left pulmonary artery. Anticoagulant therapy with enoxaparin 100 ui/kg b.i.d. was first started, followed after three days by long-term warfarin (PT/INR range 2-3, target 2.5). Patient was investigated for inherited and acquired thrombophilia and tested positive only for antiphospholipid antibodies (Table II). Seven days after the diagnosis of pulmonary embolism (eleven from admission) he was discharged in good clinical conditions (anti-MP antibodies titre: 1:640). At three months follow-up, patient was asymptom-

atic. Laboratory tests [anti-nuclear antibodies (ANA), antiphosholipid antibodies, D-Dimer] were within normality, as well as echocardiography and Doppler US-scan. Anti-mycoplasma antibodies titre was reduced (1:40).

Discussion

The present case describes the occurrence of VTE in a young male patient with no pre-existing diseases, affected by fever and cough, due to MP infection, without evidence of pneumonia, nor respiratory failure, nor reduced motility.

Should this Patient Receive Pharmacological Prophylaxis for VTE?

According to literature, the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in acutely ill medical patients is 0.8% and 0.4%, respectively[9]. Moreover, the risk for VTE is higher in certain categories of patients (e.g., cancer, history of previous VTE, reduced motility, known thrombophilia, recent trauma or surgery, age >70 yrs., heart or respiratory failure, acute myocardial infarction or stroke, obesity and hormonal treatment) which require VTE prophylaxis[10]. Padua Prediction Score was 1 (low risk for VTE)[10], and the International Society on Thrombosis and Haemostasis bleeding scale was 0 (low bleeding risk)[11]. Our patient had been considered at low risk and, in turn, did not receive any VTE prophylaxis.

Could Lab Tests Suggest Any Risk Factor for VTE?

As reported in Table II, lab tests were showing an acute inflammatory state, as procoagulant risk factor. However, the patient did not have any reduction in motility, he was not bedridden nor affected by respiratory failure.

Why this Patient Developed VTE?

According to literature data, VTE, in particular PE, represents a rare event during MP infection[4]. However, this assumption should be taken with caution because the frequency of VTE in patients with MP infection could reach 50% in fatal cases, as well as it could be under- or un-diagnosed in non-fatal cases[12]. To the best of our knowledge, 16 cases of PE during MP infection have been reported in the English literature (Table III). A total of 15 patients had signs of pneumonitis, 8 patients died due to fulminant disease (respiratory and multiorgan failure). Six out of sixteen patients had cold agglutinins, at least 6 patients showed the presence of anti-cardiolipin antibodies and 4 were positive for lupus anticoagulant test (Table III). Interestingly, only one patient (case 8, Table III) was diagnosed with PE in the absence of pneumonia at chest standard X-ray, even if chest CT-scan was not performed[22]. Finally, one patient (case 16, Table III) developed saddle pulmonary embolism despite adequate VTE prophylaxis[4].

MP represents an intracellular pathogen with peculiar characteristics of virulence, such as cyto-adherence, mobility and direct cytotoxicity[8]. Although pathogenesis has not been completely defined, main mechanisms of disease are:

- **Direct:** cyto-adhesion to membrane cells, such as those of respiratory tract (responsible for pulmonary manifestations), erythrocytes (direct hemolysis) and probably other organs (liver and central nervous system) induces direct cytotoxicity with consequent activation of local inflammatory cascade due to the presence of microorganism in the site of inflammation[13].
- **Indirect:** immune-mediated disease due to autoimmunity through cross-reaction between human cells and the bacterial cell components and vascular occlusion due to vasculitis with blood flow obstruction[13].

The indirect mechanism has been suggested to be responsible for most of the extrapulmonary manifestations of MP infection through an autoimmune reaction and molecular mimicry. This triggers the production of antibodies against phospholipids, glicolipids and proteins[8,13,14], with associated vasculitic/thrombotic disorders both in presence or not of systemic hypercoagulable state. Several infectious diseases (viral, bacterial) have been associated to a transient or permanent rise of antiphospholipid antibodies[7]. Our patient showed the presence of lupus anticoagulant and anti-cardiolipin antibodies during the acute phase, subsequently normalized at three months follow-up. The "pro-thrombotic" effect of anti-phospholipid antibodies is linked to several mechanisms, such as cellular activation (direct stimulation of endothelial cell procoagulant activity; enhancement platelet activation and aggregation), inhibition of endogenous anticoagulants (including protein C, protein S, anti-thrombin, and annexin A5), impairment of fibrinolysis and complement activation[15].

Table III. Cases of mycoplasma pneumoniae associated pulmonary embolism reported in the English literature.

		pt	M. pneumoniae diagnosis	Clinical evolution	Chest X-ray	Diagnosis of PE	Lower limb Doppler	Lupus anticoagulant	Anti-cardiolipin antibodies	Anti-beta-2 glycoprotein antibodies	Other
1	Maisel et al[16]	70 F	Post-mortem culture	Death	n.a.	Autopsy	n.a.	n.a.	n.a.	n.a.	Hemolytic anemia, cold agglutinins, multiple organs thromboembolism; CNS involvement
2	Sterner et al[17]	45 M	Post-mortem	Death	Right sided pneumonia	Autopsy	n.a.	n.a.	Positive	Positive	CNS involvement
3	Fraley et al[18]	28 F	n.a.	Death	Bilateral lung infiltrates	Autopsy	n.a.	n.a.	n.a.	n.a.	-
4	Benisch et al[19]	23 M	Immunofluorescence	Death	Right middle lobe consolidation	Autopsy	n.a.	n.a.	n.a.	n.a.	Parainfluenza co-infection
5	Meyers et al[20]	56 F	Complement fixation	Death	Lung infiltrates	Autopsy	n.a.	n.a.	n.a.	n.a.	-
6	Mardh et al[21]	68 F	IgM	Death	Pneumonia (autopsy)	Autopsy	n.a.	n.a.	n.a.	n.a.	DVT; cold agglutinins; acute pancreatitis
7	Koletsky et al[22]	30 F	Post mortem cultures	Death	Diffuse bilateral lung infiltrates	n.a.	n.a.	n.a.	n.a.	n.a.	-
8	Murayama et al[23]	48 F	Ig +	Dyspnea and haemolytic anemia	No lung infiltrates	Lung scintigraphy	n.a.	n.a.	n.a.	n.a.	Direct Coombs Test; cold agglutinins
9	Jimenez et al[12]	38 F	IgM + IgG+	Asthenia, hearing loss	Interstitial pattern at right lower lobe	Lung scintigraphy	Negative	n.a.	n.a.	n.a.	Bilateral otitis media
10	Brown et al[15]	6 M	IgM+	Worsening hypoxia	Pneumonia, pleural effusion	Chest CT scan	DVT	Positive	IgM+ IgG+	n.a.	Acquired activated C protein resistance, cold agglutinins
11	Graw-Panzer et al[24]	13 M	IgM+ IgG+	Worsening	Pneumonia, hypoxia and fever	Chest pleural effusion	DVT CT scan	Positive	IgM+	n.a. IgG+	Low protein S levels, cold agglutinins

Table Continued

Table III *(Continued)*. Cases of mycoplasma pneumoniae associated pulmonary embolism reported in the English literature.

		pt	M. pneumoniae diagnosis	Clinical evolution	Chest X-ray	Diagnosis of PE	Lower limb Doppler	Lupus anticoagulant	Anti-cardiolipin antibodies	Anti-beta-2 glycoprotein antibodies	Other
12	Senda et al[25]	21 M	Ig +	Aphasia, right emiparesis	Bilateral interstitial pneumonia	Brain MRI and TEE: paradoxycal embolism (stroke due to PFO)	DVT	Positive	IgM+	n.a.	Slightly decreased protein C activity
13	Ascer et al[26]	28 M	Ig +	Chest pain, dyspnea	Right lower lobe pneumonia (CT)	Lung scintigraphy, chest CT scan	n.a.	Positive	Igm+ IgG+	n.a.	ANA +
14	Chen et al[27]	12 F	Ig +	Chest pain and tachypnea	Left lower lobe pneumonia	Lung scintigraphy, chest CT scan	DVT	n.a.	Ig +	n.a.	-
15	Zhuo et al[28]	9 M	IgM +	Respiratory failure, death	Bilateral patchy pneumonia (CT)	Chest CT scan	DVT	n.a.	n.a.	n.a.	-
16	Chilet et al[4]	75 F	IgM+ IgG+	Severe respiratory failure	Bilateral lung infiltrates	Chest CT scan	n.a.	n.a.	Negative	n.a.	Decreased protein C activity; cold agglutinins

Conclusions

To the best of our knowledge, this is the only case of PE during MP infection without pneumonia. A direct (endothelitis due to MP endothelial infection) or indirect (antibodies due to molecular mimicry) endothelial damage could explain the occurrence of PE in those patients with no known risk factors for VTE. Clinicians should outweigh risk and benefits for LMWH prophylaxis case by case considering these adjunctive pro-thrombotic mechanisms in patients with infectious diseases[29], particularly in those with MP Infection.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethical Approval

The patient has given written consent to the case report in anonymized form.

Authors' Contribution

AM, AL, MD and SC managed the patient. EG made the laboratory assays. AM, AL, MD and EG thought for the rationale of the research. AM, AL and MD made the bibliographic research. AM, GV, EG and SDC wrote the first draft. All the Authors had access to the full paper, read and approved the final version of the manuscript.

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