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Community acquired pneumonia and pulmonary thromboembolisms in a Chinese child

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Introduction

In Hong Kong, previous study by using complement fixation method found the commonest pathogen of respiratory diseases under 11 years old was *Mycoplasma pneumoniae* (31.5%), followed by respiratory synticial virus, adenovirus and parainfluenza type 3.[1] A case of mycoplasma pneumonia complicated by bilateral pulmonary embolism was presented.

Case

A five-year-old boy presented with fever, 39° Celcius, and cough for 2 days. He enjoyed good past health. There was no travel or contact history. Family history was unremarkable. On admission, his respiratory rate was 28 per minutes and SpO_2 was 97%. Physical examination showed that he was well hydrated and there were crepitations over bilateral chest. Chest X-ray (CXR) showed right perihilar streakiness on admission. Complete blood picture showed white blood cell 8.9, neutrophil 6.1 and lymphocyte 1.5. C-reactive protein was 22.6 mg/L. Cold agglutinin titre was <64. Blood culture showed no growth.

Clarithromycin was started on admission. Intravenous amoxicillin-clavulanic acid was started the day after admission. Fever persisted, he was lethargic and his appetite was poor. Intraveous fluid was required. CXR (Figure 1) on day 3 showed right upper lobe consolidation, Mantoux test was negative. Amoxicillin-clavulanic acid was changed to intravenous tazocin on day 4. CT thorax with contrast was booked on day 7 and done on day 9 because of persistence of fever and white-out right upper lobe. However, CT thorax showed no empyema and instead showed pulmonary embolisms at bilateral lower lobe's pulmonary arteries and right upper lobe consolidation. Enoxaparin was started on the same day. He was stable clinically and his fever became lower, though he developed herpes simplex virus type 1 oral ulcers on day 17. Fever pattern and serial blood tests results were shown in Chart 1. IgG for mycoplasma showed a 16 fold increase in titer subsequently. His fever finally subsided on day 19 admission. Enoxaparin was switched to oral warfarin. Blood test results at one month were normal: white blood cell 7.7, neutrophil 3.2, lymphocyte 3.0, C-reactive protein 2.42, D-dimer 72. Protein C, protein S, antithrombin III and anti-cardiolipin antibody serum levels were normal. Lupus anti-coagulant was detected. Echocardiogram and ultrasound doppler of lower limb were normal. Anti-coagulation therapy was given for six months. Follow up test for lupus anti-coagulant was negative. He was well on follow up at time of writing which was 2 years after the event.

Discussion

For children with pneumonia, culture of sputum or nasopharyngeal aspirates yielded predominant or pure growth of one bacterial agent in only 17% of cases. The commonest bacterial agents were *Haemophilus influenzae,* followed by *Streptococcus pneumoniae* and *Staphylococcus aureus.*[2] The incidence of pneumonia requiring admission to the hospital was 6.4 episodes per 1,000 children per year for those <5 years of age.[2] On the other hand, data in other countries suggested the incidence of first episode pneumonia in unimmunised children younger than five years of age was 55.9 per 1000 person-years and in those up to 15 years of age, *Streptococcus pneumoniae* accounted for between 17% and 28% of all community-acquired pneumonia cases and it was suggested that the use of the heptavalent conjugate pneumococcal vaccine reduced chest X-ray positive pneumonia by up to 20%.[3] It was important to note that causative agents of pneumonia may change with the universal vaccination program against pneumococci.

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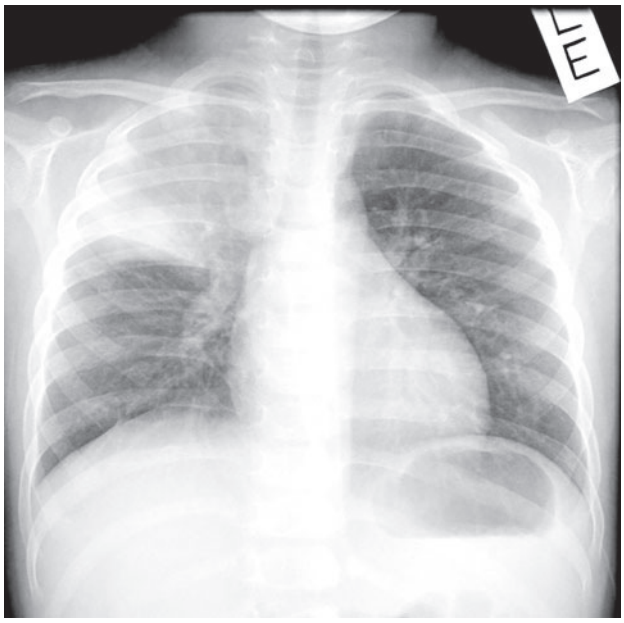
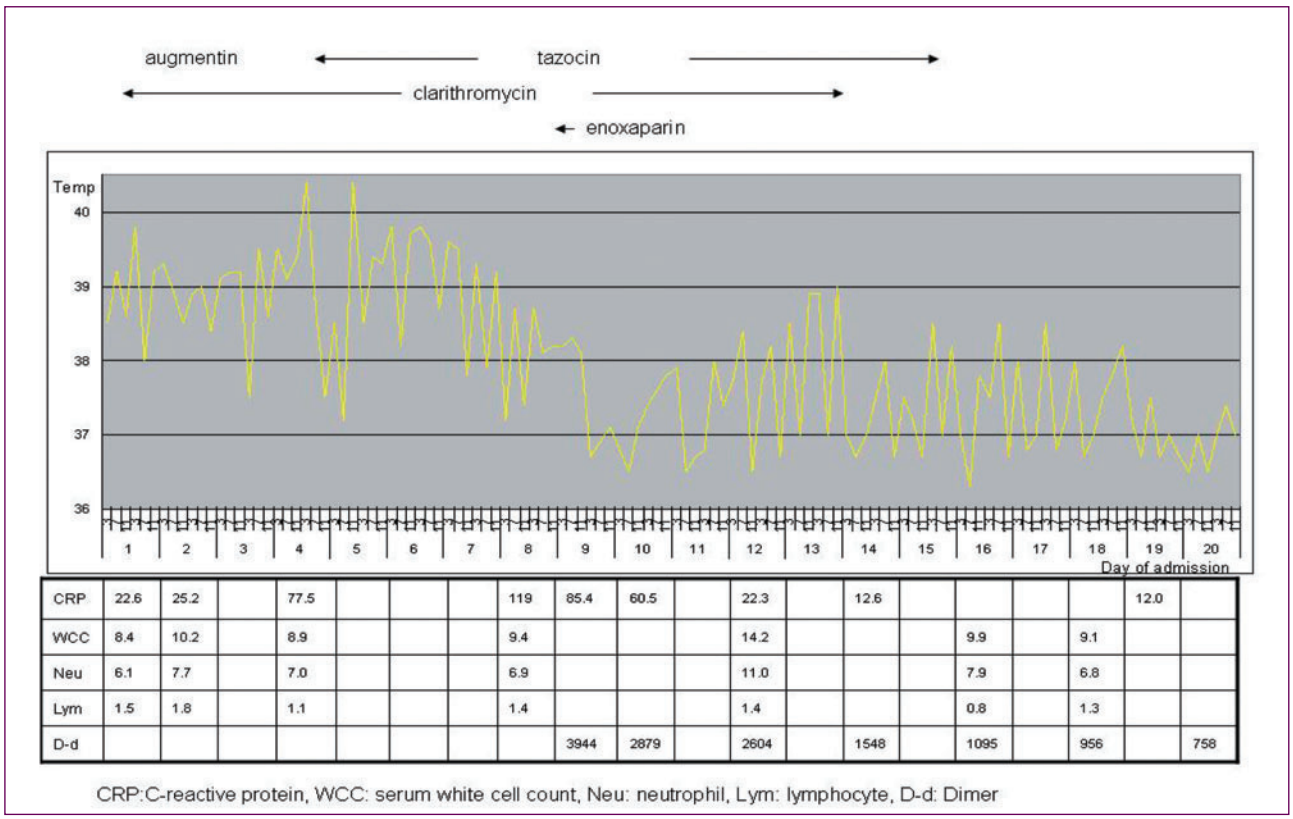


Figure 1. Chest X-ray.

In the current case, the causative agent is one of the commonest agents, *Mycoplasma pneumoniae*. Macrolide was given but fever persisted. In adult studies, treatment failure in community acquired pneumoniae may be defined as lack of response or clinical deterioration and defined as early when it occurs within the first 72 hours and late when it occurs after 72 hours. Among hospitalised patients with CAP, treatment failure ranges from 2.4 to 31% for early failure and from 3.9 to 11% for late failure.[4] There is no universal definition to define treatment failure. Roso'n et al defined early failure as lack of response or worsening of clinical or radiological status at 48 to 72 hours of treatment requiring changes in antibiotic therapy or invasive procedures and the commonest cause was progressive pneumonia which was defined by radiological progression.[5] Arancibia et al defined non-responding pneumonia as persistent fever >38°C and/or clinical symptoms (including malaise, cough, expectoration and dyspnoea) after at least 72 hours of antimicrobial



CRP	22.6	25.2		77.5				119	85.4	60.5		22.3		12.6				12.0	
WCC	8.4	10.2		8.9				9.4				14.2				9.9		9.1		
Neu	6.1	7.7		7.0				6.9				11.0				7.9		6.8		
Lym	1.5	1.8		1.1				1.4				1.4				0.8		1.3		
D-d									3944	2879		2604		1548		1095		956		758

CRP:C-reactive protein, WCC: serum white cell count, Neu: neutrophil, Lym: lymphocyte, D-d: Dimer

Chart 1. Temperature chart and serial investigation results.

treatment.[6] Most cases of early failure occurred because of inadequate host-pathogen responses.[4] Causes of treatment failure may be divided into infectious and non-infectious causes. For infectious causes, *Streptococcus pneumoniae, Legionella, Staphylococcus aureus, and Pseudomonas aeruginosa* were associated with treatment failure. For non-infectious causes, drug-induced pneumonitis, aspiration of gastric contents, adult respiratory distress syndrome, pulmonary embolism, carcinomatous lymphangitis and cardiogenic pulmonary oedema had been identified. Serum C-reactive protein is a useful marker, persistently high or rising CRP levels suggest antibiotic treatment failure or the development of complications. CRP concentration above 50% of the initial value on day 3 of therapy was associated with poor outcome and higher mortality.[7]

In this case, thromboembolism may be the cause of treatment failure. Thromboembolism in children was uncommon, 0.05-14 per 10,000 children,[8] with one peak in neonates and infants, another peak in puberty and adolescence. Sandoval et al showed increasing incidence of thromboembolism in paediatric intensive care unit patients, from 0.3/10,000 admissions in 1992 to 28/10,000 admissions in 2005.[9] Congenital risk factors include deficiency of proteins C, S, or AT-III; gene mutations: Factor V Leiden, Prothrombin G20210A; hyperhomocystinemia; elevated lipoprotein(a); congenital cyanotic heart disease and sickle cell disease. Acquired risk factors include infection; noninfectious inflammation; dehydration; diabetes; nephritic syndrome; mechanical compression; central venous catheter; trauma; polycythemia/hyperviscosity; Lupus anticoagulant; antiphospholipid antibodies; anti-beta2-glycoprotein I antibodies; drugs: L-asparaginase, oral contraceptives, antifibrinolytic agents, prednisone, coagulation factor concentrates. Upper limb venous thrombosis is more common in children, likely associated with upper limb central venous catheter. However, transient lupus anticoagulants were often detected in association with infection in children and did not appear to represent a risk for thrombosis.[10] For pulmonary embolism, there is no validated screening algorithm in children and investigations are based on suspicion of paediatricians. Monagle et al showed that 56% of pulmonary embolisms were associated with thrombosis at another location.[11] In children, pulmonary embolisms are often silent unless there is comorbid cardiopulmonary disease or emboli obstructing more than fifty percent of the pulmonary circulation.[12] Classic symptoms of a pulmonary embolisms, shortness of breath, pleuritic chest pain, and hemoptysis, are usually absent and children may have difficulties in expressing their chest discomfort. In children, persistent tachypnoea out of proportion to clinical picture may be an important clue of pulmonary embolisms. For investigations of pulmonary embolisms, a low D-dimer level in adult is safe to exclude pulmonary embolism in patients with a low clinical suspicion of pulmonary embolisms.[13] So, screening by D-dimer level may be useful in children who are previously healthy. Pulmonary angiography is the traditional investigation but limited by the invasiveness of the test. Ventilation perfusion scan is a useful screening test but the test interpretation can be affected by the underlying cardiopulmonary diseases. Helical computed tomography can detect other chest anomalies and adult study showed sensitivity from 53 to 100%, and specificity ranged from 81 to 100% in detecting pulmonary embolisms.[14] Magnetic resonance angiography is another useful imaging but long examination time may not be suitable for unstable patients. Ultrasound Doppler is useful in detecting deep venous thrombosis of lower extremities. Echocardiography is useful to rule out intra-cardiac and major pulmonary arteries emboli and look for right ventricular dilatation.

Management of pulmonary embolisms depends on the clinical condition of the patients. Anticoagulation therapy should be given in haemodynamically stable patient. Thrombolytic therapy should be considered in haemodynamically unstable patient. Unfractionated heparin is used for initial anticoagulation. A higher dose is required in infant and children due to a larger volume of distribution. Side effects include bleeding and heparin induced thrombocytopenia. Clotting profile should be monitored. Nowadays, an alternative is low molecular weight heparin which has advantages such as less monitoring, no need for venous access, decrease interference with other drugs or diet and reduced risk of thrombocytopenia. Monitoring of anti-factor Xa level should be considered during use of low molecular weight heparin. Anticoagulation therapy is usually bridged to oral warfarin. For prognosis, a meta-analysis showed that in children, recurrent venous thromboemobolisms were found in those with protein C, protein S, antithrombin deficiency and the factor II variant, though not observed in those with the factor V variant or elevated lipoprotein(a).[15]

In conclusion, thromboembolism is a rare complication of mycoplasma pneumonia which may not be obvious clinically in children. CT-thorax helps to elucidate the causes of treatment failure in children with pneumonia.

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