American Journal of Medical Case Reports, 2017, Vol. 5, No. 1, 15-21
Available online at http://pubs.sciepub.com/ajmcr/5/1/5

DOI:10.12691/ajmcr-5-1-5

Mycoplasma Pneumoniae, an Important Differential Diagnosis of Non-Responding Pneumonia

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Abstract A 24-year-old Chinese lady presented with 2 weeks of fever and 1 week of cough to us after being given antibiotic by the primary care physician. Chest-X-ray showed left sided pneumonia. She undergone computed tomography of chest and bronchoscopy to investigate the non-responding pneumonia. The final diagnosis of Mycoplasma pneumoniae pneumonia (MPP) was made after the serology result turned out to be positive. Despite having being given 11 days of macrolide, she failed to achieve clinical stability till day 13 of her admission. This case demonstrated the atypical features of MPP and the importance to consider MPP as one of the differentials of non-responding pneumonia.

Keywords: *non-responding pneumonia, mycoplasma pneumoniae, macrolide resistance*

Cite This Article: Chaozer Er, "Mycoplasma Pneumoniae, an Important Differential Diagnosis of Non-Responding Pneumonia." *American Journal of Medical Case Reports*, vol. 5, no. 1 (2017): 15-21. doi: 10.12691/ajmcr-5-1-5.

1. Introduction

Community acquired pneumonia (CAP) is a common acute medical condition that leads to hospitalization [1]. In the United States, pneumonia is the 6th leading cause of death and the number one cause of death from infectious disease [2]. Mortality rate is 1 to < 5% and 12% in outpatient setting and in patients who require hospitalisation respectively [2]. Most patients with CAP respond to treatment but some may not [1]. They end up requiring further investigation and prolonged hospital stay. Appropriate early intervention can improve outcome of patients with non-responding pneumonia [1]. It is therefore prudent to assess for clinical response in patients with CAP and be aware of possible aetiologies of non-responding pneumonia. I present a case of non-responding pneumonia caused by Mycoplasma pneumoniae to illustrate these.

2. Case Report

A 24-year-old Chinese lady with no past medical history presented to us with 2 weeks of fever associated with 1 week of cough. Chest X-ray performed by the general practitioner showed left lung consolidation. She has completed 3 days of Azithromycin followed by another 3 days of Co-amoxiclav. The persistent fever led to her admission.

She was given intravenous (IV) Co-amoxicalv and oral Clarithromycin as community acquired pneumonia treatment. As pulmonary tuberculosis was one of the differentials, she was isolated till her sputum were negative of Acid Fast Bacillus (AFB) stain. A computed tomography (CT) of her chest was performed after de-isolation. It showed extensive left lung consolidation (Table 1). As fever persisted, the antibiotics were changed to IV Piperacillin-tazobactam, IV Vancomycin and oral Clarithromycin on day 4 of admission after consulting our respiratory medicine physician. A bronchoscopy was performed (Table 1) and it showed white cheesy plaque at the trachea, left main bronchus and purulent secretion from left upper lobe. Antibiotic was changed to IV Ceftazidime, IV Vancomycin and oral Clarithromycin on day 6 of admission after consulting our infectious disease physician. Vancomycin was stopped on day 8 of admission when blood cultures were negative. She completed 8 days of oral Clarithromycin.

The fever resolved on day 12 of admission (Table 2). On the same day, the meliodosis serology which was sent on day 4 of admission tuned out to be positive at 1:16 titre. She was discharged on day 16 of admission with follow up with our outpatient-antibiotic-service to complete 2 weeks of IV Ceftazidime as presumptive meliodosis treatment. However, the mycoplasma IgG titre came back positive at >640 after her discharge, Ceftazidime was stopped and she was given another 1 week of Azithromycin. The final diagnosis was mycoplasma pneumoniae pneumonia (MPP).

3. Discussion

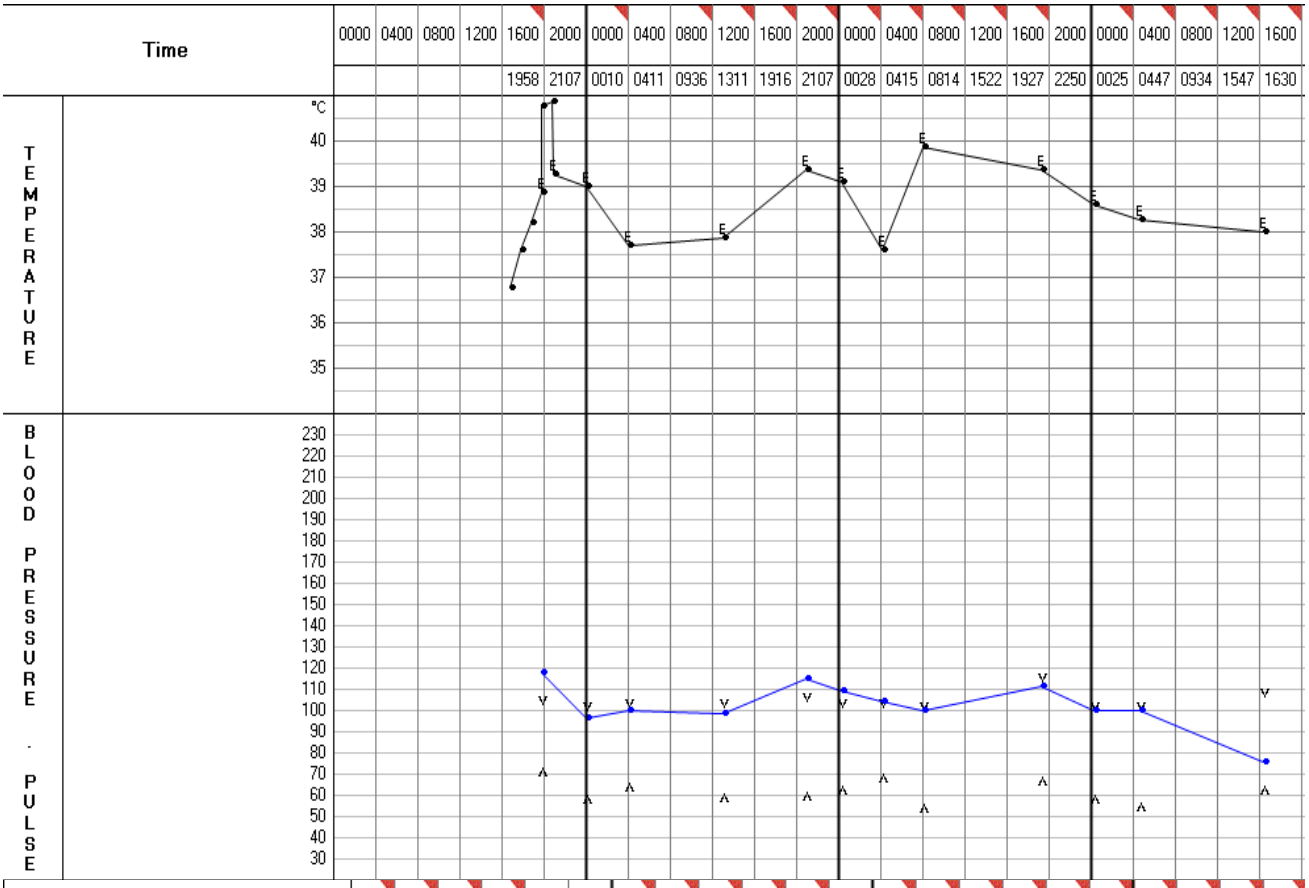
Non-responding pneumonia was described as failure to achieve clinical stability as defined by the Halm's criteria in the expected period of time with appropriate treatment[1]. The Infectious Disease Society of America/ American Thoracic Society (IDSA/ATS) 2007 guidelines recommend

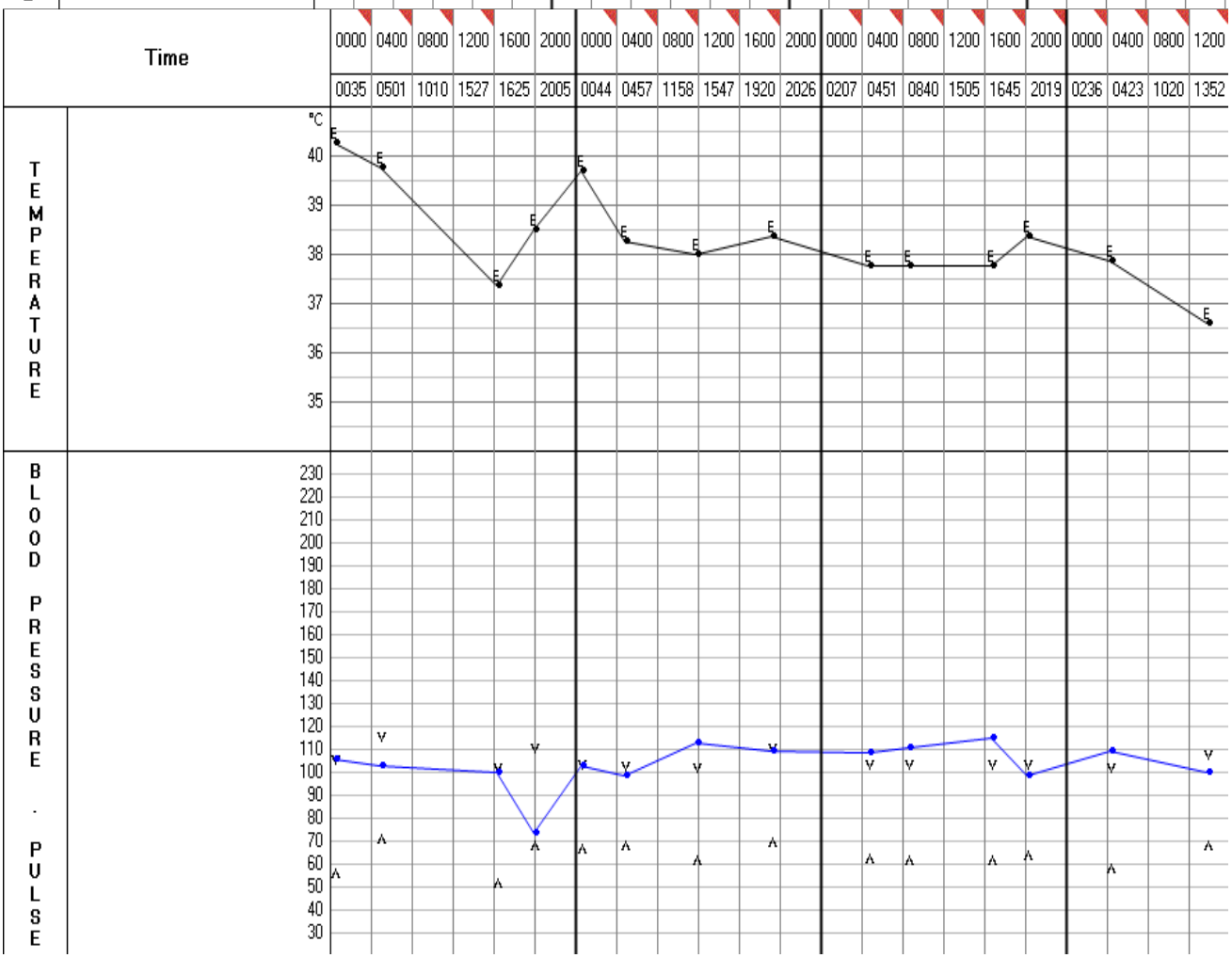
using the Halm's criteria to determine clinical stability [1]. Halm's criteria include temperature ≤ 37.8°C, heart rate ≤ 100 beats/minute, respiratory rate ≤ 24 breaths/minute, systolic blood pressure ≥ 90mmHg, O_2 saturation ≥ 90% or arterial O_2 tension ≥ 60mmHg, normal mental status and normal oral intake [1]. All criteria must be met to define clinical stability [1]. 3 days is the median time to reach clinical stability [1]. One study showed that median time to resolution of fever and dyspnoea were 3 and 6 days respectively [3]. Our patient had non-responding pneumonia as she did not achieve clinical stability till day 13 of admission when her fever and tachycardia resolved. She however did not require supplemental oxygen throughout the admission despite the significantly reduced effort tolerance.

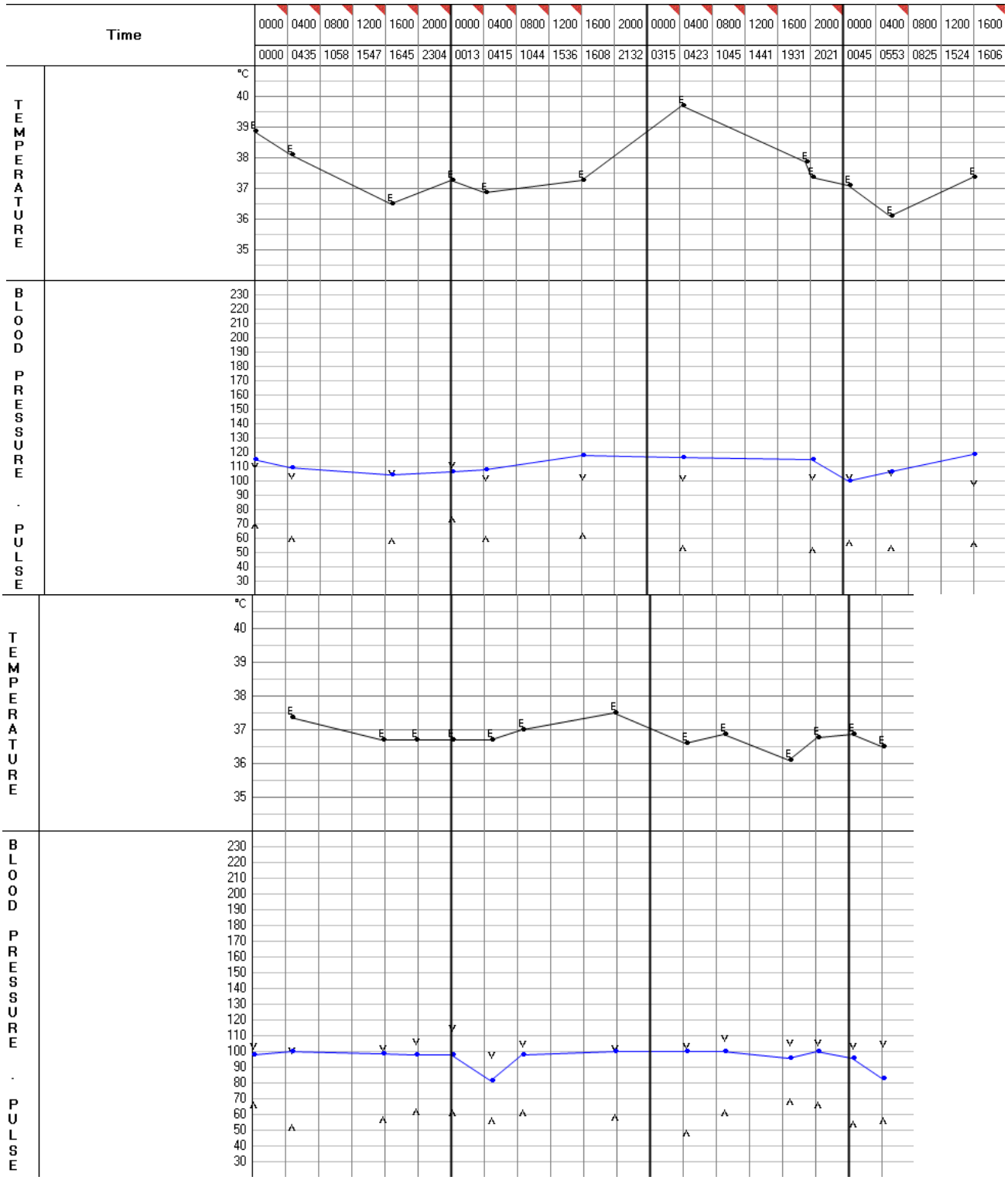
Table 1. Relevant Investigations

Investigation	Result	Reference
White cell (on admission)	5.5 x 10^9/L	3.6-9.3 x 10^9/L
Haemoglobin (on admission)	12.9 g/dL	11-15 g/dL
Platelet (on admission)	196 x 10^9/L	170-420 x 10^9/L
C-reactive protein (on admission)	320 mg/L	0-5 mg/L
HIV screen	Negative	
HbA1c	5.7%	Ideal 4.5-6.4%
Sputum acid fast bacillus stain (AFB) x 4 sets	Negative	
Sputum Mycobacterium tuberculosis PCR	Negative	
Blood culture on admission x 2 sets	No growth	
Blood culture on day 4 of admission x 2 sets	No growth	
Urine Legionella antigen	Negative	
Urine Streptococcus pneumoniae antigen	Negative	
Influenza PCR	Negative	
Sputum Gram stain	Predominant organism not seen	
Nasal swab respiratory viruses multiplex PCR	Negative	
Burkholderia pseudomallei antibody	Indirect haemagglutination assay (IHA) titre 1:16 Positive	
Bronchial washing		
1) Gram stain	No predominant organism	
2) Culture	Normal flora of the upper respiratory tract	
3) Microscopy	No Nocardia isolated after prolonged incubation 308 nucleated cells/uL 85% neutrophils 4% lymphocytes 1% monocytes 1% eosinophils 9% macrophages	
4) Aspergillus galactomannan test	Negative	
5) Fungus smear and culture	Negative	
6) Cytology	No malignant cells	
7) Gomoris Methenamine-Silver Nitrate stain for Pneumocystis jiroveci	Negative	
8) Acid fast bacillus stain	Negative	
9) M. tuberculosis PCR	Negative	
Bronchoscopy	Vocal cords normal. White cheesy plaques seen in trachea and left main bronchus. Consider fungal infections. Purulent secretions from left upper lobe seen. No significant secretions in right bronchial tree	
Computed tomography of chest	1. Extensive consolidation, peribronchial cuffing and centrilobular nodularity is seen in the left lung, in keeping with the submitted history of infection. Similar, milder infective changes are seen in the right lung. 2. A small left parapneumonic effusion is seen. 3. Reactive mediastinal and hilar lymphadenopathy are noted	
Computed tomography pulmonary angiogram	There is no pulmonary embolism	
Ultrasonography of abdomen	No collection or abscess	

Table 2. Temperature, blood pressure and heart rate charting







The simplified American Thoracic Society (ATS) criteria consist of improvement in cough and shortness of breath, absence of fever >37.8°C for > 8 hours, normalisation of leukocyte count by 10% from the previous day and adequate oral intake have been proposed as an alternative to Halm's criteria[1]. Aliberti et al. however showed that it may be less sensitive compared to Halm's criteria [1,4].

Aliberti et al showed that the prognosis was good: no in-hospital deaths and haemodynamically unstable patient, only 1.2% of respiratory complications once clinical stability was chieved [1,4]. Studies conducted in the U.K., U.S.A and Spain also reported similar result [1]. It is therefore important to assess for clinical stability in patients with pneumonia.

Kashyap et al. mentioned that fever lasts about 1 week in uncomplicated MPP and symptoms duration are shorter if antibiotics are commenced early [5]. Our patient's fever lasted for 26 days in spite of being given 3 days of Azithromycin and 8 days of Clarithromycin. Her tachycardia persisted till day 13 of admission (Table 2). Her dyspnoea resolved only after the extra 7 days of oral Azithromycin. These are atypical of MPP.

One of the possible reasons of her slow recovery may be macrolide resistance. Macrolide resistance in Mycoplasma

pneumoniae was reported to be 95% and 13.2% in China and the U.S.A. respectively [6,7]. A study in France showed that macrolide resistant Mycoplasma pneumoniae was on the rising trend: 9.8% between year 2005 to 2007 compared to 0% before year 2005 [8]. My literature search failed to identify macrolide resistance rate of Mycoplasma pneumoniae in Singapore. Suzuki et. al however showed that there was no apparent treatment failure or serious events in patients with macrolide resistant Mycoplasma pneumoniae infection treated with macrolide [9]. They were shown to have more febrile days (by median of 2 days) compared to macrolide sensitive patients [9].

Shorter duration of macrolide treatment was probably another reason of her slow recovery. Azithromycin 10mg/kg/day for 5 days or Clarithromycin 15mg/kg/day in 2 divided doses for 10-15 days was the widely accepted treatment[5]. Our patient was given 3 days of Azithromycin at a dose of 500mg daily followed by another 8 days of Clarithromycin 500mg twice daily initially. Longer treatment may have been helpful. Soon after her discharge and knowing the Mycoplasma serology result, she was given another 1 week of Azithromycin. Her dyspnoea resolved at the end of the treatment.

The meliodosis serology turned out to be weakly positive before the Mycoplasma serology result was known and the fact that her fever showed improvement (Table 2) with Ceftazidime supported the initial diagnosis of meliodosis. Serology is inadequate in confirming the diagnosis of meliodosis as it can be falsely positive in endemic regions [10]. Diagnosis is mainly based on positive culture of B. pseudomallei from any clinical sample [10]. Unfortunately, our patient's sputum and blood culture were negative. Direct polymerase-chain-reaction assay of a clinical sample can provide rapid diagnosis but it is not widely available including at our hospital [10]. The turnaround time of meliodosis serology in our hospital is about 6 days. These made diagnosis of meliodosis difficult as Singapore is considered one of the endemic regions [8].

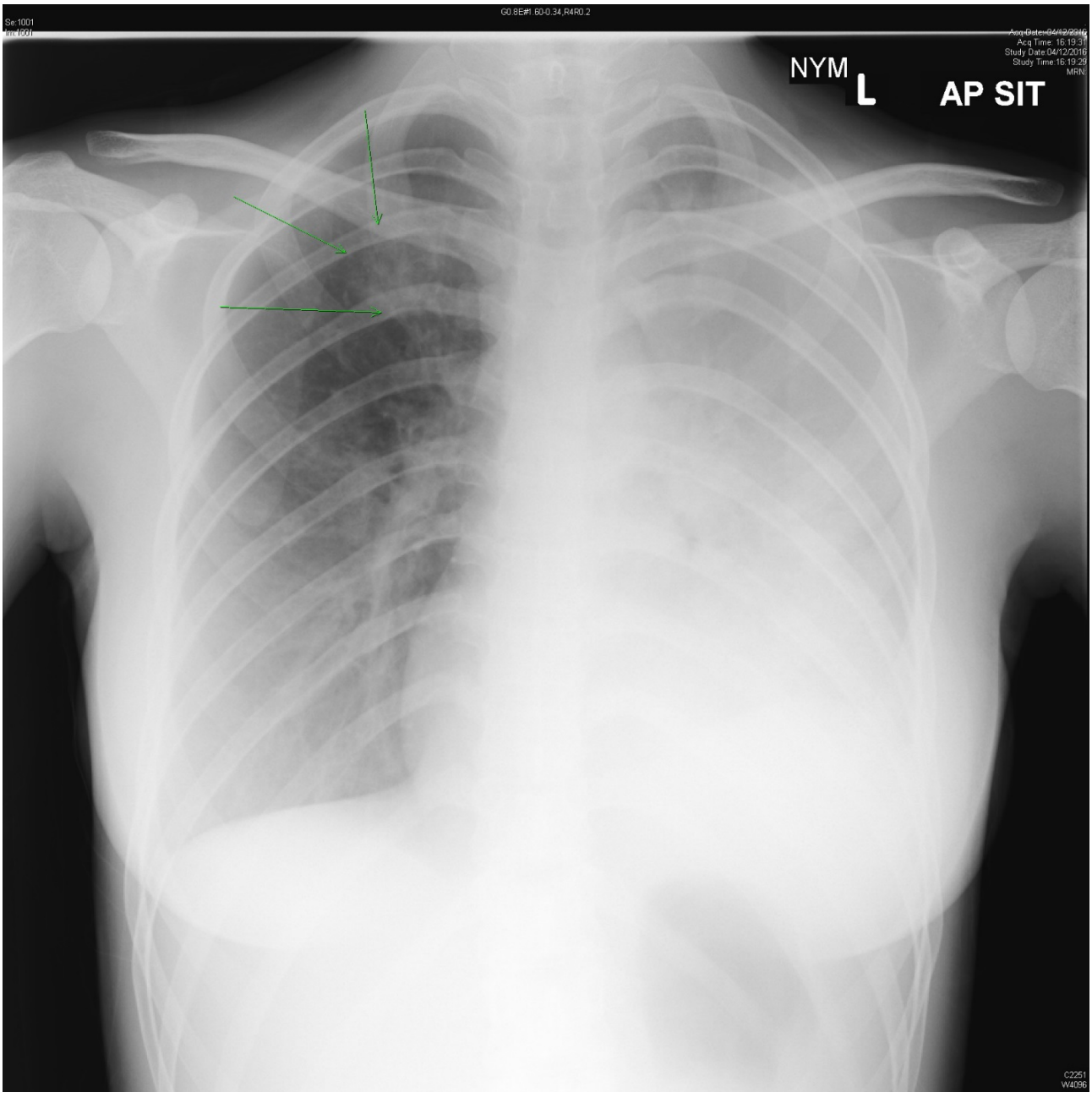


Figure 1. Patient's chest X-ray on admission

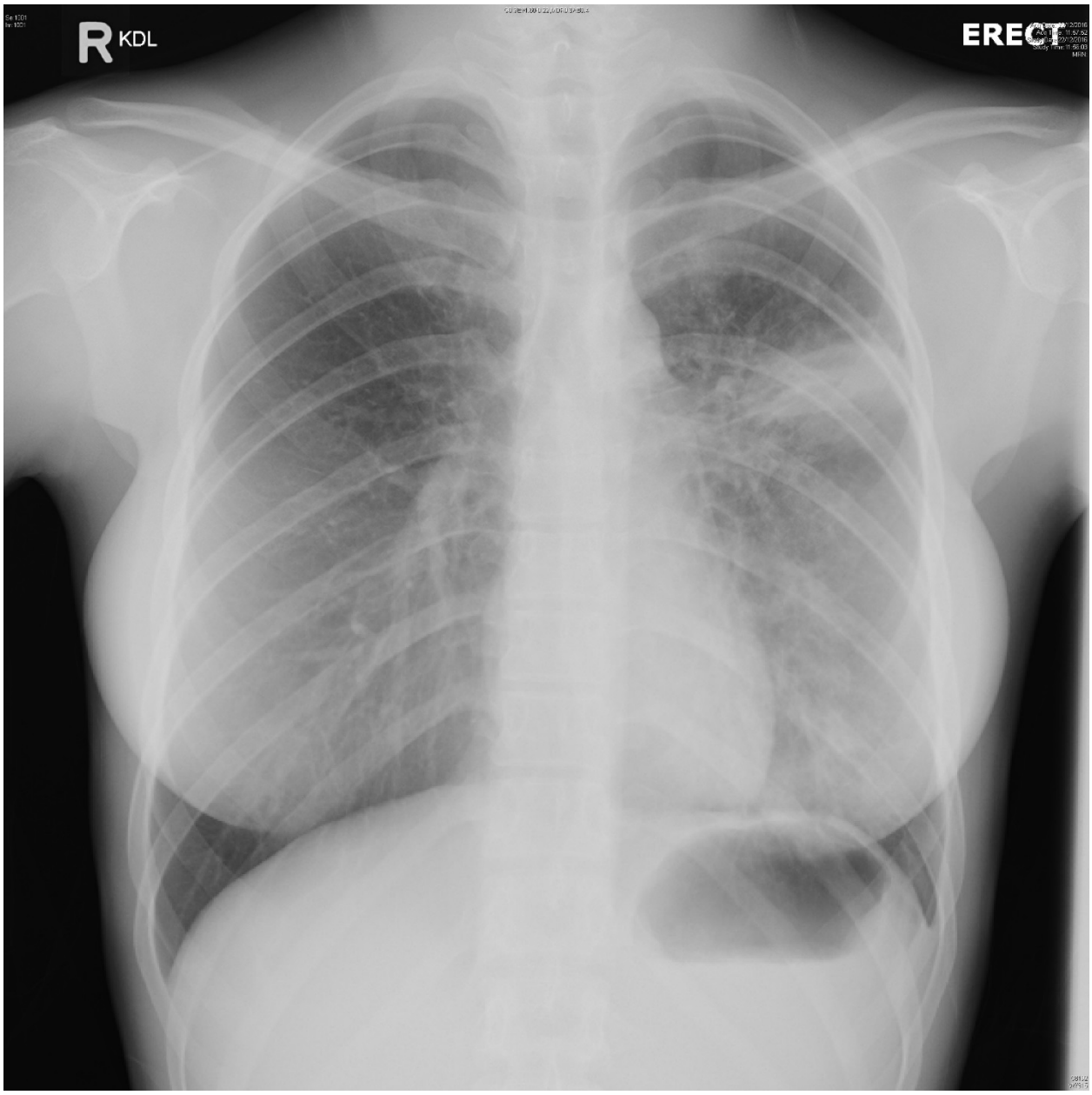


Figure 2. Patient's chest X-ray 1 week after discharge

Important causes of non-responding pneumonia include multidrug resistant pathogens, tuberculosis, empyema or lung abscess and non-infectious causes such as pulmonary embolism, lung cancer or vasculitis [1]. Our patient had no symptoms or signs suggestive of connective tissue disease. CT pulmonary angiogram and CT chest showed no pulmonary embolism, abscess, empyema or cancer.

In conclusion, it is important to consider Mycoplasma pneumoniae as one of the differentials of non-responding pneumonia as it can present atypically like our case. A good course of macrolide should be given to all patients with non-responding pneumonia. It is also vital to include meliodosis treatment as part of the empirical treatment for non-responding pneumonia especially in endemic regions knowing that melidosis diagnosis can be challenging.

Acknowledgements

Nil.

Conflict of Interest

Nil.

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