

37th Clinical Infection & Public Health Forum

A man developed confusion after  
the death of his pet

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20/7/2010

# Patient

- M/56
- Divorced, living with 2 daughters
- Non-smoker
- Non-drinker
- worker in electronic warehouse
- NKDA

# Past medical history

- Left frontal parasagittal meningioma with excision done in 2003
- General anxiety disorder on prothiaden fu YFS psychiatric OPD
  - Last fu 9/09: mentally stable

- Patient started to have fever since 13/11/2009
  - Coincident with the death of his pet (a parrot bought from Mongkok “bird street” on 6/11/2009)



- Family members unaffected
- Patient was admitted to UCH on 23/11/2009

# Present illness

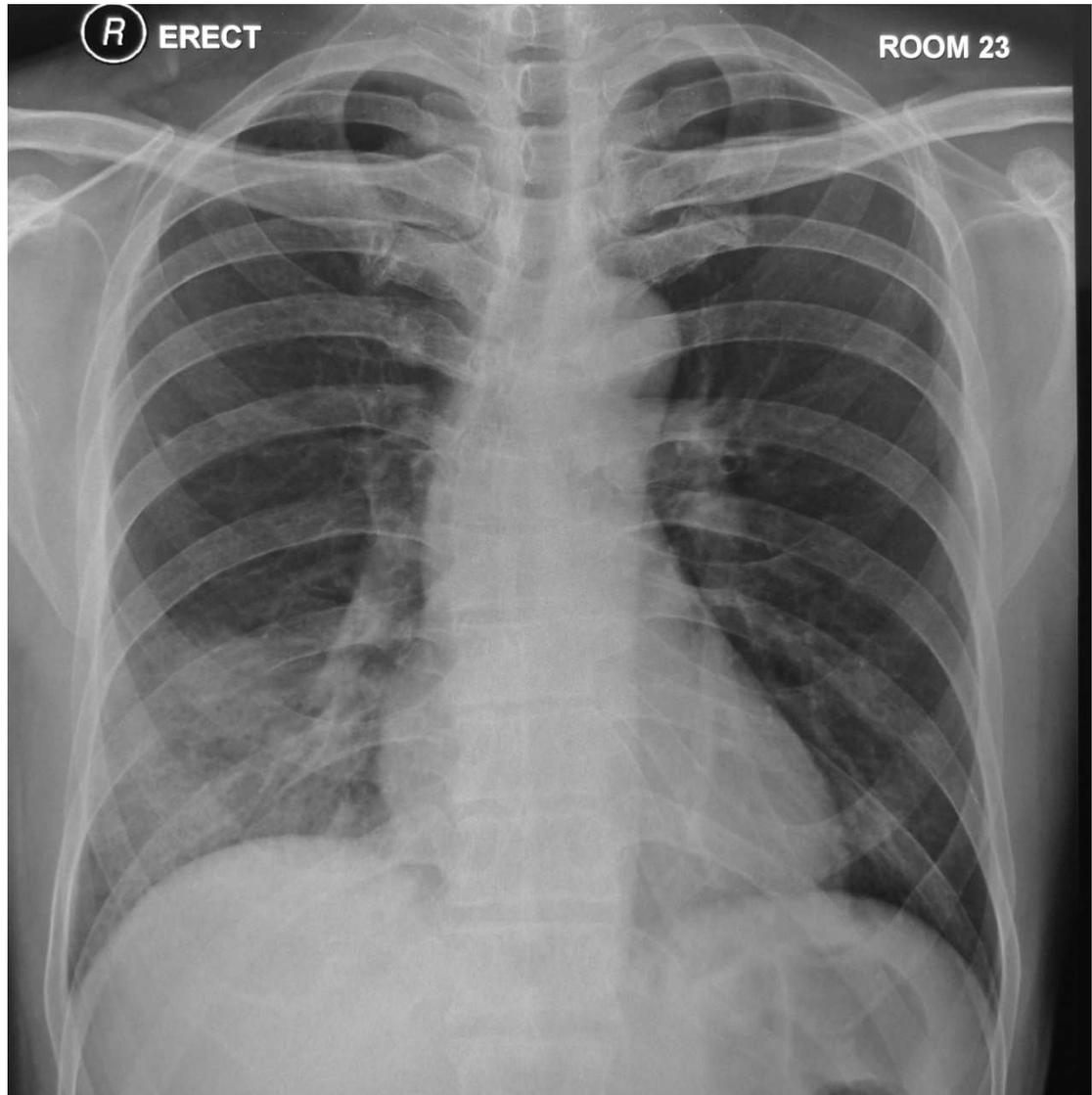
- c/o Fever for 10 days
- No respiratory or GI symptom
- No recent travel

# Physical exam on admission

- Temperature 39.9 degree Celcius
- BP 119/67, pulse 105
- SaO2 97% room air
- Chest: RLZ crepitation
- Cardiac, Abd and neurological exam: normal

CXR on admission

- RLL hazziness



# Initial Ix results

- CBP
  - Hb 13.2
  - Wcc 5.4
    - (N 4.1, L 0.8, M 0.4, E 0.0)
  - Plt 299
  - ESR 41
- RFT
  - Na 132
  - K 3.7
  - Urea 2.9
  - Creat 78
- Bili 4
- ALP 46
- TP 60
- Alb 29
- Glo 31
- AST 42
- ALT 12
- Ca 1.91
- PO4 0.91
- LDH 220
- CK 220
- TnT <0.03

# Differential diagnosis

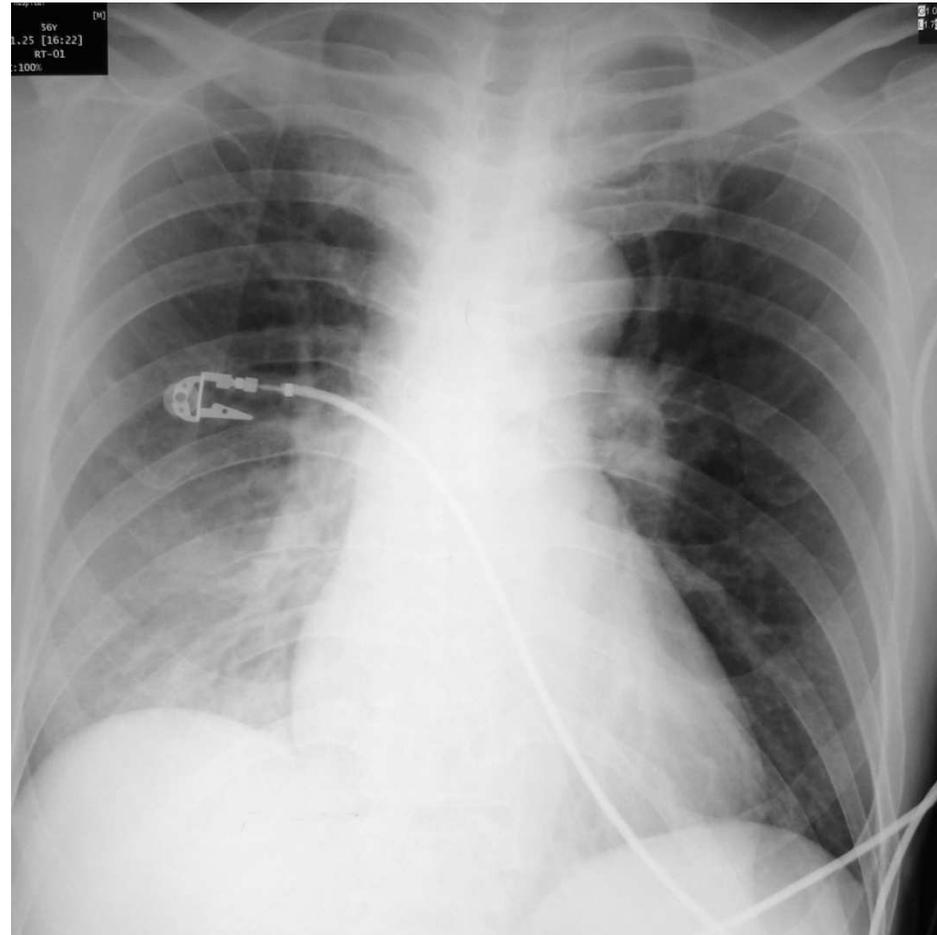
- Community acquired pneumonia
- Human Swine flu
- Avian flu (H5N1)

# Empirical treatment

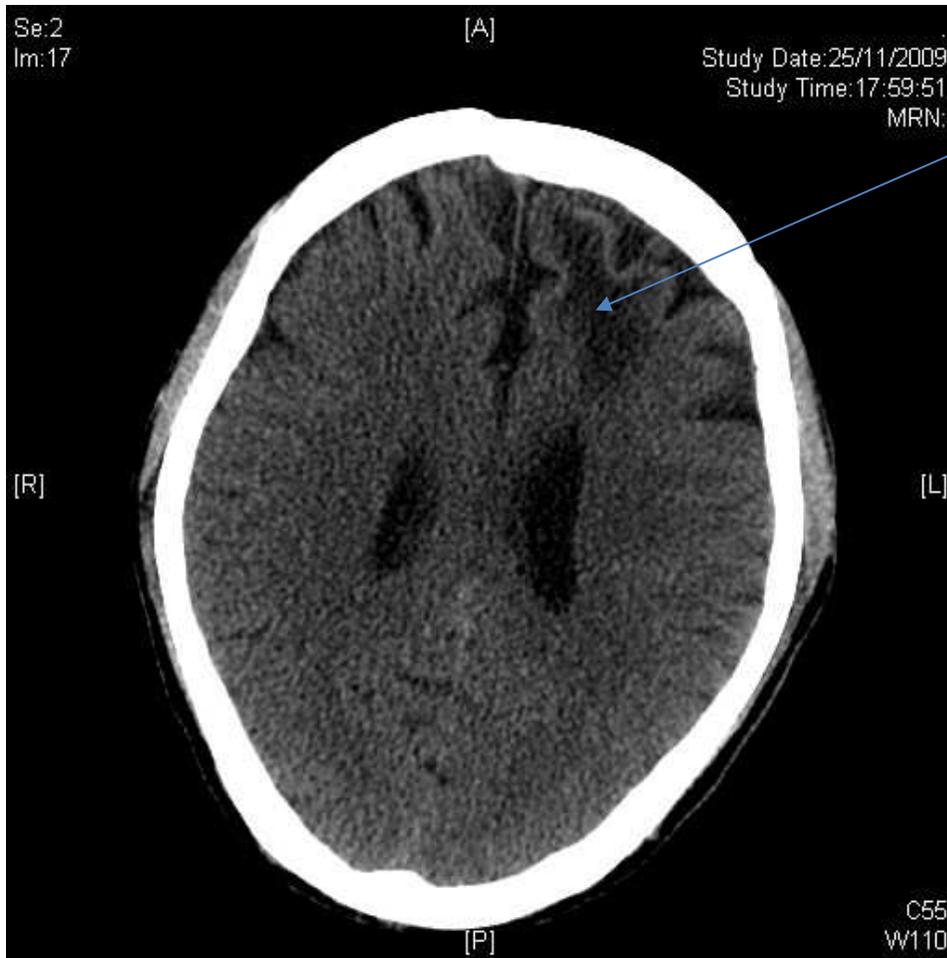
- 23/11/2009
  - Ceftriaxone (Rocephin) iv
  - Doxycycline po
  - Clarithromycin (Klacid) po
  - Oseltamivir (Tamiflu) po
- 24/11/2009
  - Ceftriaxone (Rocephin) iv
  - Azithromycin iv
  - Oseltamivir (Tamiflu) po +  
Zanamivir (Relenza)  
inhaler
  - Amantadine

# Developed confusion

- 24/11/2009 night:
  - ‘non-attentive’
- 25/11/2009:
  - Mental dullness, slow response
  - Crying, refused to move
  - Still high fever



# CT Brain



Plain CT brain:  
Wedge shape  
hypodensity in  
left frontal lobe,  
similar to old CT  
3/2009

# DDx for confusion

- CNS infection
- CNS complication of influenza
- Drug (amantadine/oseltamivir/zanamivir) induced confusion
- Psychiatric illness

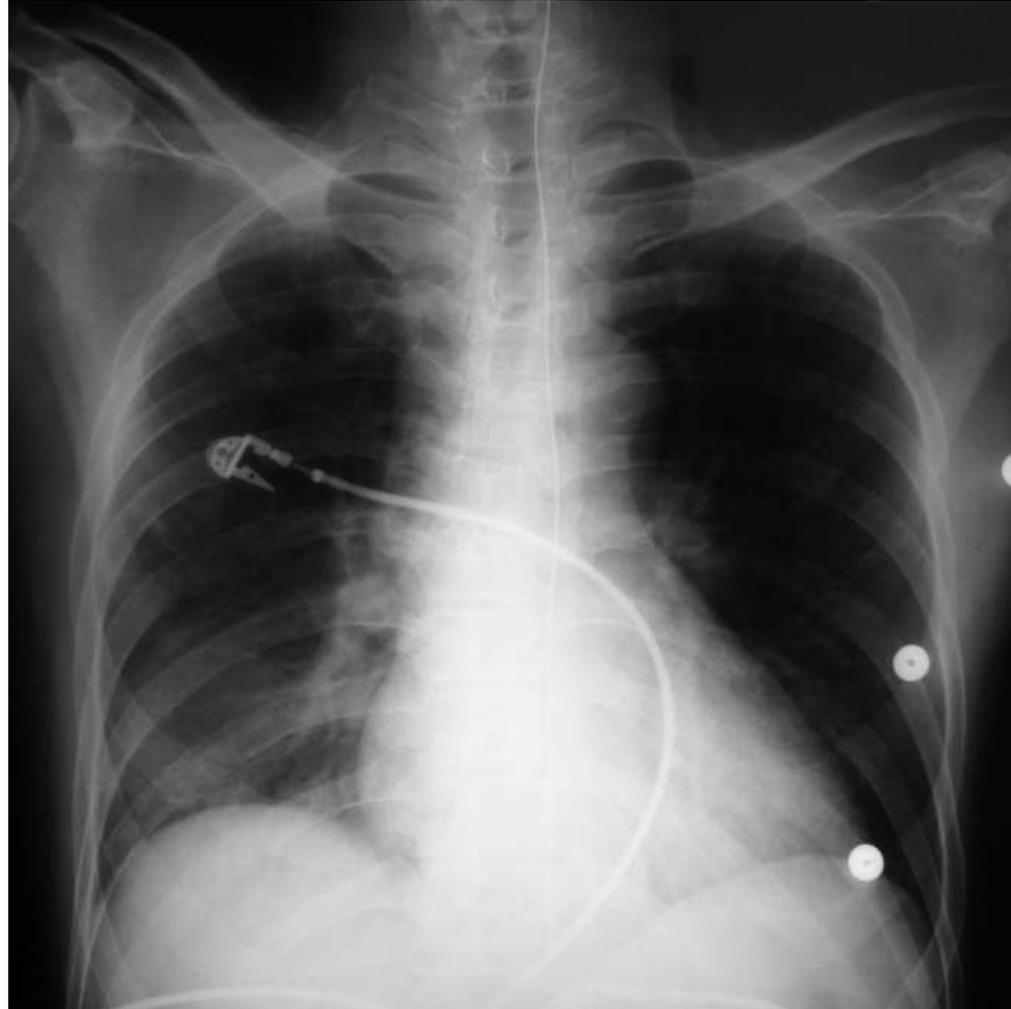
- 25/11/2009:
  - NPA for influenza A/B Ag ; RT-PCR HSI: –ve
    - Stopped tamiflu, amantadine, relenza
  - Psychi:
    - Dx: Acute confusion, possibly drug induced, + haldol prn

# Still confused, normal LP

- 26/11/2009 (Day 4):
  - Still high swinging fever
  - LP:
    - Opening pressure 17cmH<sub>2</sub>O, clear CSF
    - Wcc 1/mm<sup>3</sup>, Rbc <1/mm<sup>3</sup>
    - CSF glucose 3.6 (6.6), protein 201
    - Gram stain –ve
  - Stepped up rocephin to meropenem, IV azithromycin continued

# Improving CXR but no change in mental status

- 27/11/2009:
  - CXR: improving RLL consolidation
  - Still fever
  - Mental state same



# Noticed to have bilateral eye redness

- Opinion from ophthalmologist: filamentary keratitis
- Given hypromellose and cravit eye drop



# Important result came back...

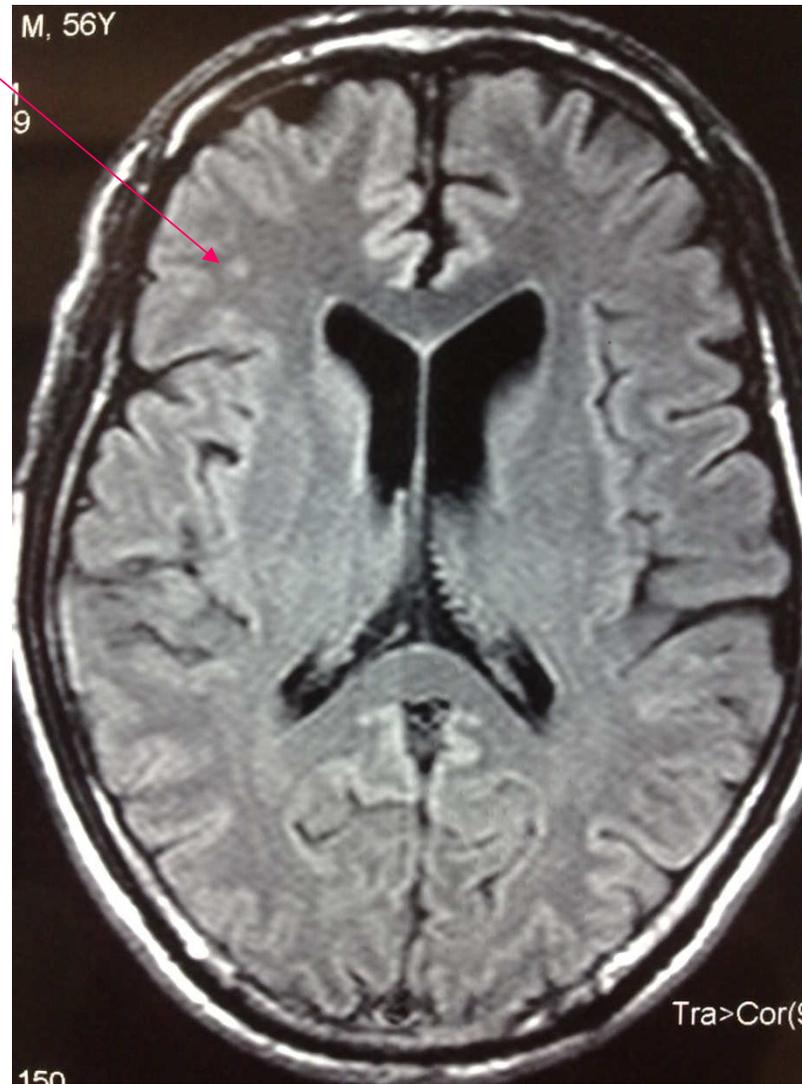
- NPA PCR for *Chlamydophila psittaci* +ve
- Infectious Diseases Team was consulted for persistent fever and confusion
  - ID team opinion: change iv azithromycin to po doxycycline (via R/T)

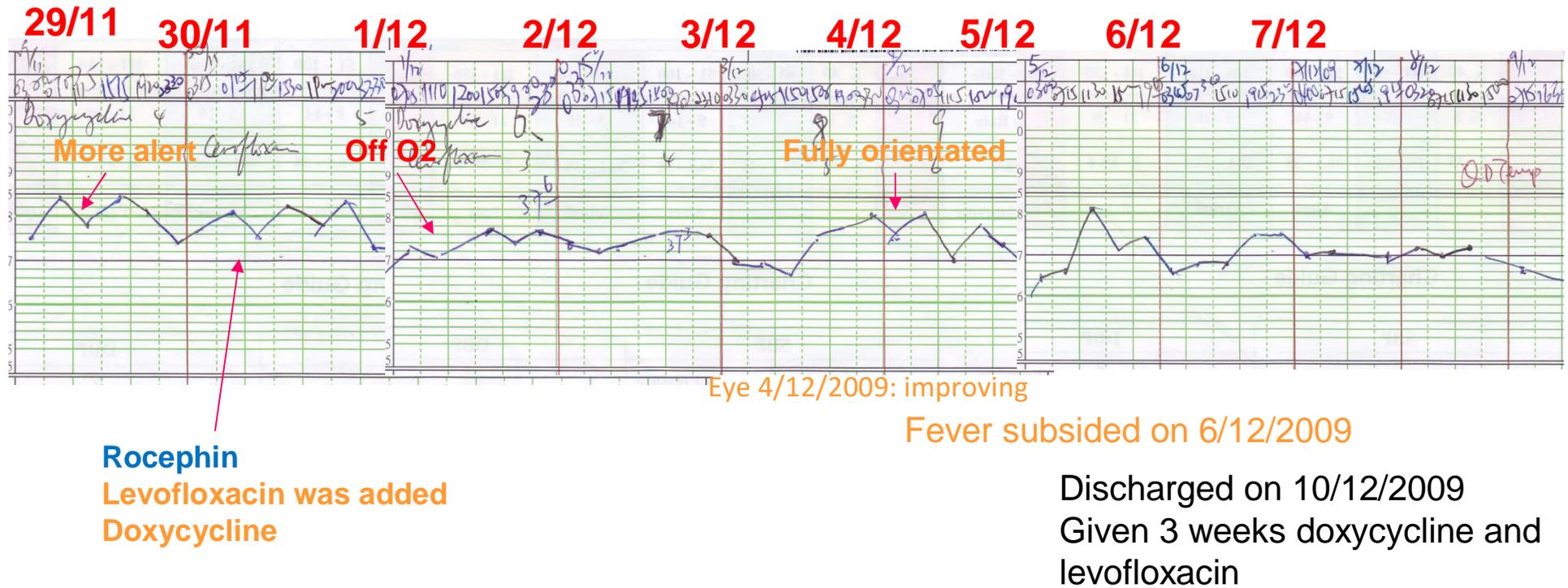
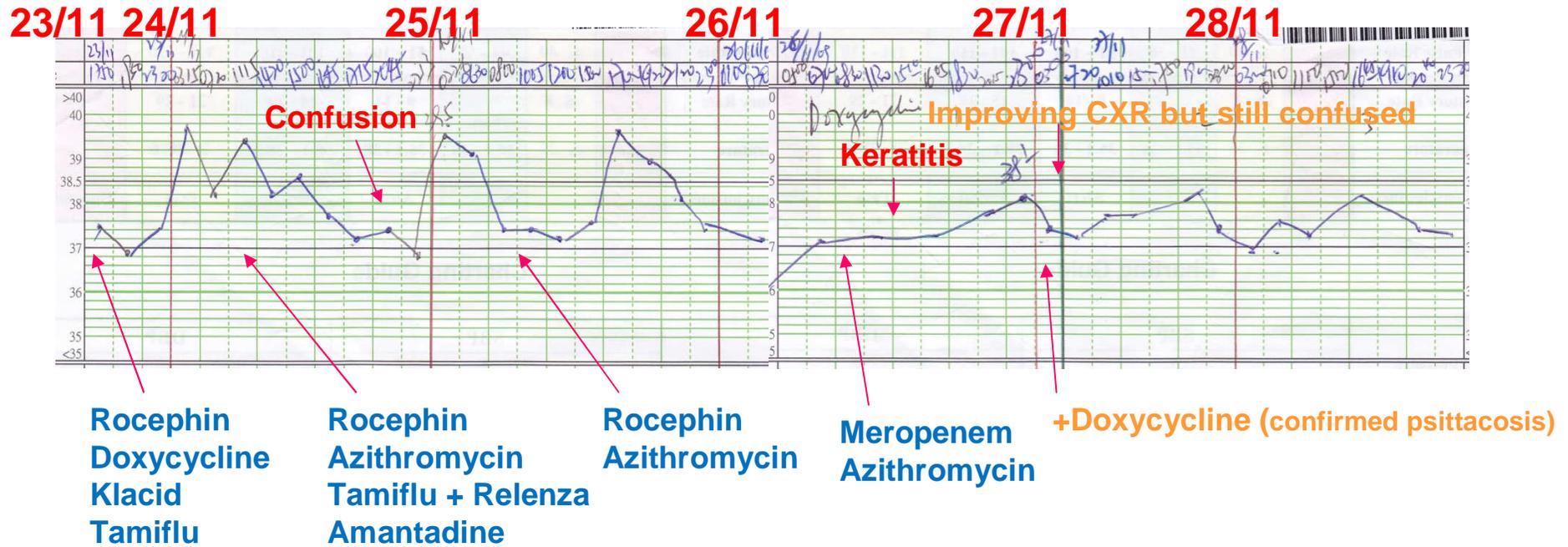
# Further workup for confusion

- EEG:
  - background slow wave
  - intermittent sharp waves predominantly over bilateral frontal regions
  - Suggestive of underlying diffuse cerebral dysfunction/encephalopathy
- CSF PCR for *chlamydophila psittaci* –ve

Multiple small foci showing low T1, high T2 and FLAIR signals are detected at the right frontal lobe, suggestive of nonspecific white matter changes.

MRI brain with  
contrast  
3/12/2009





# >4 fold elevation in titre

## Antibody Titre - Serum

Lab No	V09-2134225	V09-2135076
Date	24/11/2009	03/12/2009
Influenza virus type A	20	20
Influenza virus type B	20	20
Adenovirus	< 10	< 10
Chlamydia group	40 	320 
Mycoplasma pneumoniae	< 10	< 10
Parainfluenza virus type 1	< 10	< 10
Parainfluenza virus type 2	< 10	< 10
Parainfluenza virus type 3	10	10
Respiratory syncytial virus	10	10
Legionella pneumophila	< 32	< 32

Rising antibody titre to chlamydia indicative of recent infection. Please correlate with clinical features.

# Summary

- Psittacosis
- Presented with pneumonia, severe CNS involvement + keratoconjunctivitis
  - Normal CSF
  - Non-specific change in MRI
- Pneumonia improved with azithromycin but confusion persisted
- Confusion improved with doxycycline +/- levofloxacin
- Fever finally subsided 13 days after admission

# Topic review

**Table 1**  
**Taxonomy of the *Chlamydiales* order**

<b>Order</b>	<b>Family</b>	<b>Genera</b>	<b>Species</b>	<b>Typical Host</b>	<b>Previous Taxonomy</b>
Chlamydiales	Chlamydiaceae	<i>Chlamydophila</i>	<i>C abortus</i>	Mammals	<i>Chlamydia psittaci</i>
			<i>C psittaci</i>	Birds	
			<i>C felis</i>	Cats	
			<i>C caviae</i>	Guinea pigs	
			<i>C pecorum</i>	Mammals	<i>C pecorum</i>
			<i>C pneumoniae</i>	Humans	<i>C pneumoniae</i>
		<i>Chlamydia</i>	<i>C trachomatis</i>	People	<i>C trachomatis</i>
			<i>C suis</i>	Swine	
			<i>C muridarum</i>	Mice, hamsters	
			Parachlamydiaceae		<i>P acanthomaebae</i>
	Waddiaceae		<i>W chondrophila</i>		
	Simkaniaceae		<i>S negevensis</i>		

Data from Bush RM, Everett KDE. Molecular evolution of the *Chlamydiaceae*. In J Syst Evol Microbiol 2001;51:203–20.

Stewardson AJ, Grayson ML.

Infect Dis Clin North Am. 2010 Mar;24(1):7-25. Review.

# *Chlamydophila psittaci*

- Non-motile, Gram-ve, obligate intracellular bacteria with unique biphasic life cycle
- Divided into eight serovars according to variation in the major outer membrane protein (MOMP)
  - eight corresponding genotypes based on the sequencing of variable domains of the outer membrane protein A (ompA) gene were defined

Table 2 Serotypes and genotypes of <i>Chlamydophila psittaci</i>			Most common
Serovar	Genotype	Predominant Host Order: Examples	Human Infection Documented
A	A	<b>Parrot</b> Psittaformes: budgerigars, cockatiels, parakeets	Yes
B	B	Columbiformes: pigeons, doves	Yes
C	C	Anseriformes: ducks, geese, swans	Yes
D	D	Galliformes: turkeys, pheasants, chickens	Yes <sup>97</sup>
E	E	Struthioniformes: ostriches, pigeons, duck	Yes <sup>22</sup>
F	F	Isolated from single parakeet and turkey only	Yes <sup>97</sup>
WC	G	Cattle	
M56	H	Rodents	
	E/B <sup>4</sup>	Ducks	Yes <sup>97</sup>

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# Psittacosis

- Also known as parrot fever or ornithosis
- A zoonotic infection caused by *Chlamydophila psittaci*
- *Despite its name, C psittaci infection has been documented in 467 species from 30 bird orders, from psittaformes to ostriches to penguins*

- Budgerigar (彩鳳)



- , cockatiels

(葵花鸚鵡)



parakeets (small parrot, 長尾鸚鵡)



macaws 金剛鸚鵡



and pigeons are most

frequently involved

- Most infection in birds are asymptomatic. Conjunctivitis and diarrhoea are the most common signs in birds

# Routes of transmission to human

- Human inhales organisms that have been aerosolized from dried feces or respiratory tract secretions of infected birds
- Handling infected birds' plumage and tissues
- Mouth-to-beak contact

# Epidemiology and transmission

- ~25% patients had no reported avian exposure
- Person-to-person transmission is possible, but it is believed to be rare
- Although psittacosis can affect any age group, the incidence peaks in middle age, between the ages of 35 and 55
- Incubation period ranges from one to four weeks, typically 5-14 days

# Incidence in HK

In HK:

- 1 case in 2005 (seen in PMH)
- 1 case in 2007

## A case of Psittacosis (Parrot fever)

On February 22, 2005, the Centre for Health Protection (CHP) confirmed a local case of psittacosis (parrot fever) involving a 40-year-old lady. She presented with cough, shortness of breath and confusion in mid-January 2005. On January 22, she was admitted to the intensive care unit of a hospital with a diagnosis of myocarditis (Creatinine Phosphokinase 270219 U/L, normal range 42-245 U/L; Lactic Dehydrogenase 6193 U/L, normal range 110-230 U/L; Troponin I 67.5  $\mu\text{g/L}$ , normal range  $< 1\mu\text{g/L}$ ; ECG showed no acute ischaemic changes), acute renal failure (creatinine 357  $\mu\text{mol/L}$ , normal range 60-120  $\mu\text{mol/L}$ ; Base Excess -12.5 mmol/L, normal range -2 to +2  $\mu\text{mol/L}$ ), and rhabdomyolysis. She was put on mechanical ventilation, inotropic support, and intermittent haemodialysis. Her chest x-ray was clear and she did not have any rash on admission. Empirical broad spectrum antibiotics and antiviral including Clarythromicin, Tazocin, and Doxycycline, and Oseltamivir were given at different stages of her illness. Paired sera taken on January 23 and February 2 showed raised antibody titres to *Chlamydophila* antigens (from  $<1:10$  to 1:320). The diagnosis of psittacosis was confirmed on February 22 when a throat swab of the patient taken on admission was retrieved and was tested positive by polymerase chain reaction (PCR) and gene sequencing. The patient is now in stable condition.

According to investigations by the CHP and the Agriculture, Fisheries and Conservation Department (AFCD), the patient was a security guard with no travel history in the past six months. Since late November 2004, she bought and kept three pet birds at home. They were two budgerigars (彩鳳) and one cockatiel (葵花鸚鵡). There was otherwise no history of close contact with birds. Her two family contacts were asymptomatic during the period of medical surveillance. The pet birds did not show signs of sickness on inspection. They were surrendered voluntarily to AFCD for testing. Swabs taken on the conjunctiva of the cockatiel tested positive for *C. psittaci* by direct immunofluorescence staining and cloacal smears from this bird were positive by specific PCR test for *C. psittaci*. The two budgerigars were negative on both tests.



Photos of Budgerigars (above) and Cockatiel (below)



# Incidence in HK

- Included as a notifiable disease in HK since 14 July 2008 under Prevention and Control of Disease Ordinance
- Our case was the first notified case

# Clinical features of Psittacosis

Disease severity can range from subclinical infection to fulminant sepsis with multiorgan failure in previously healthy individuals, which may occasionally be fatal despite appropriate treatment.

- Abrupt onset of fever (50-100%), chills, headache, myalgia (30-70%), malaise
- Respiratory symptoms are frequently mild or absent on presentation.
  - Non-productive cough
  - Shortness of breath, chest tightness

# Clinical features of Psittacosis (that may be present)

- GI symptom such as vomiting, diarrhoea and abdominal pain
- Pulse-temperature dissociation (fever without ↑ pulse rate), non-specific rash, splenomegaly
- Pneumonia, endocarditis, myocarditis, hepatitis, arthritis (reactive), keratoconjunctivitis, meningoencephalitis, ocular adnexa lymphoma, thrombocytopenia, acute interstitial nephritis, acute renal failure

# Clinical features of Psittacosis (that may be present)

- Severe illness with ARDS, respiratory failure, multi-organ failure
- Pregnant women: atypical pneumonia, hepatitis, renal insufficiency, sepsis, premature birth or fetal death
- Can present as pyrexia of unknown origin (PUO)
- Fatality with appropriate treatment ~1% (20% without Rx)

# Psittacosis and pneumonia

- CXRs are abnormal in up to 90% of hospitalized cases
- Most commonly unilateral LL dense consolidation
- Also bilateral, nodular, miliary or interstitial infiltrates
  - Aust Vet J 1999;77:511-513.
  - J Comp Pathol 2003;128:217-244.

The presence of a normal chest radiograph, however, does not rule out the diagnosis of psittacosis.

# Psittacosis and CNS

- Central nervous system involvement is common
- Meningoencephalitis
  - Confusion, coma, convulsion, death
- Guillian-Barre syndrome, cerebellar disturbance, transverse myelitis, intra-cranial hypertension and cranial neuropathies have all been reported

# CNS complications

- In 20 reports of neurological complications due to psittacosis:
  - CSF in 14 cases showed:
    - lymphocytosis in 2
    - raised protein in 5
    - normal in 7
  - Clinical Infectious Diseases 1997;25:847-51.

# Pathogenesis of CNS complications

- Proposed mechanisms:
  - Direct invasion of CNS by the pathogen
  - Autoimmunological mechanisms
  - Embolic phenomena
  - Electrolyte derangement

**Comparison of the features of *Chlamydophila psittaci*, *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila* infection**

<b>Clinical Feature</b>	<b><i>C psittaci</i></b>	<b><i>C pneumoniae</i></b>	<b><i>M pneumoniae</i></b>	<b><i>L pneumophila</i></b>
Cough	++	+	++	+
Sputum	-	+	++	+++
Dyspnea	+	+	++	+++
Confusion	+	-	-	++
Chest radiograph changes	Minimal	Minimal	Disparity <sup>61</sup>	Often multifocal

Stewardson AJ, Grayson ML.  
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# Laboratory tests

- WCC:
  - usually normal to slightly lowered during acute phase
    - leucopenia ~ 25% of cases
  - Toxic granulation or left shift of neutrophils in the absence of a marked neutrophilia may be found.
- ↑ CRP/ESR, AST/ALT, GGT
- DIC, hemophagocytic syndrome (rare)

# Microbiological investigation

- Culture
- Serology (paired)
  - acute phase serum specimens: as soon as possible after onset of symptom
  - convalescent phase serum specimens: at least 2 weeks after 1st specimen
- PCR

# Culture

- Specimens: sputum, BAL, pleural fluid, blood
- Fastidious
- Risk of laboratory acquired infection
- Rarely performed

# Serology

- Complement fixation test (CF)
  - The antigen used is the lipopolysaccharide anchored to the outer membrane of all Chlamydia, including both *C psittaci* and *C pneumoniae*
  - Therefore, it is obviously not specific for *C psittaci*

# Serology

- Microimmunofluorescence (MIF)
  - utilizes species-specific chlamydial surface antigen
  - Can detect IgG or IgM
  - more sensitive and specific than CF
    - still have some cross-reactivity with other chlamydiae such as *C. pneumoniae*, *C. trachomatis*
  - N.B. antibiotic may delay or diminish antibody response → 3rd serum sample 4-6 weeks after the acute sample may be needed

# PCR

- Specimen: NPA, throat swab, sputum, BAL, blood
- Target gene:
  - 16S rRNA (performed in PHLC)
  - Outer membrane protein A (ompA) gene

# CHP case definition

- Laboratory criteria
  - Any one of the following:
    - isolation of *C. psittaci* from respiratory secretions
    - 4X rise in antibody against *C. psittaci* by CF/MIF to a titre of  $\geq 1:32$  between paired acute- and convalescent-phase serum specimens collected at least 2 weeks apart
    - detection of IgM against *C. psittaci* by MIF to a titre of  $\geq 1:16$
    - PCR +ve for *C. psittaci* in clinical specimen

# CHP case definition

- Probable case
  - A clinical compatible case that is epidemiologically linked to a confirmed case or that has supportive serology (e.g. antibody against *C. psittaci* to a titre of  $\geq 1:32$  in one or more serum specimens obtained after onset of symptom)
- Confirmed case
  - A clinical compatible case that is laboratory confirmed

# Treatment

- Doxycycline is drug of choice
  - Oral doxycycline 100mg q12h for 14 days to prevent relapse
  - IV doxycycline for severely ill patient (if available)
- Minocycline has been used clinically with success

# Macrolides

- Used in whom tetracycline is contraindicated (e.g. pregnant or children under 8 years or allergy)
  - Azithromycin 250-500mg daily for 7 days

# Quinolone

- Reports of treatment failure
- Studies on effectiveness not available
- The role of fluoroquinolones in psittacosis is not yet established

# CSF penetration

- CSF penetration:
- Doxycycline 25%
- Azithromycin <10%
- Clarithromycin <10%
- Levofloxacin 16%
- (Source : Burke A Cunha, Antibiotic Essentials 2009)

# Acknowledgement

- Dr. Kam Kwok Shing (Respiratory team, M&G, UCH)
- Dr. Steven Tseung (Microbiology Team, Pathology, UCH)

Thank you