CASE REPORT

AVIAN INFLUENZA A (H5N1) INFECTION IN A CHILD

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Abstract. A previously healthy, 9-year-old girl was admitted to the hospital with respiratory insufficiency. She had mild and severe respiratory symptoms for 3 weeks and 4 days before admission, respectively. She had a history of close contact with her domestic poultry, which was infected with avian influenza A (H5N1). She was isolated with the air-borne transmission prevention mode of treatment. Acute respiratory distress syndrome (ARDS) was documented from the time of admission and mechanical ventilation was introduced without improvement. She had multiple episodes of diarrhea for 2 days. Her condition deteriorated and she expired in 4 days. Throat swab RT-PCR and viral culture for avian influenza A (H5N1) were positive.

INTRODUCTION

A human case of avian influenza A (H5N1) infection was first documented in Hong Kong, in May 1997 (CDC, 1997). Eighteen cases with six deaths were identified by the end of 1997 (Pollack *et al*, 1998). Causes of death were respiratory and multiple organ failure (Chan, 2002). About 1.5 million chickens were rapidly culled in three days, and the outbreak was stopped (Lee *et al*, 1999; Chan, 2002). In February 2003, there were another two human cases of H5N1 with one death in Hong Kong (Peiris *et al*, 2004). By a series of genetic reassortment events, domestic ducks in southern China were found to carry the precursor of the H5N1 viruses which gave rise to the dominant H5N1 genotype Z in chickens and ducks that was responsible for the regional outbreak in 2003-2004. It is hypothesized that wild birds might have contributed to the increasingly widespread prevalence of the virus in Asia (Li *et al*, 2004). Since December 2003, avian influenza A (H5N1) infections in poultry or wild birds have been reported in 48 countries (CDC, 2006). Since then, human cases of avian influenza A (H5N1) infection has been recognized in Vietnam, Thailand, Cambodia, Indonesia, China, Turkey, Iraq, Azerbaijan, Egypt, and Djibouti. Total human cases within these 10 countries were 224 cases with 127 deaths (WHO, 2006). In Thailand, there were three episodes of avian influenza A (H5N1) epidemics in human, occuring in early 2004, late 2004 and late 2005 with case to death ratios of 12/8 (Chotpitayasunondh *et al*, 2005), 5/4 (WHO, 2005a) and 5/2 (WHO, 2005b), respectively (total 22/14).

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CASE REPORT

A previously healthy, nine-year-old girl was admitted to Petchabun Hospital on September 30, 2004. She was referred from the district hospital with severe dyspnea, on an endotracheal tube with mechanical ventilation and was suspected of avian influenza A (H5N1)

infection. Three weeks before admission she had some episodes of high fever with mild respiratory symptoms. Treatment was symptomatic. She could go to school and help her parents with their work. During this time, many poultry in her village were dead. One fighting cock from a near-by province was believed to be the carrier of avian influenza A (H5N1) virus.

A week before admission she had high fever, sore throat and cough. Eight out of ten of her poultry were dead. She helped her parents in culling the other two for food. Four days before admission she was admitted to the district hospital because of worsening symptoms. Diagnosis was pneumonia. Broad-spectrum antibiotics and supportive treatment were introduced without improvement. She was then referred to Petchabun Hospital and was placed in an isolation zone for air-borne transmission disease. She was febrile, in somnolence, slightly irritable, and neither pale or icteric. She had been inserted with an endotracheal tube with mechanical ventilation, a nasogastric tube, and Foley's catheter with a bag. Vital signs, EKG and percutaneous oxygen saturation were monitored. Vital signs: temperature 40.2ºC, blood pressure 110/60 mmHg, pulse rate 120 beats/minute and respiratory rate 40 breaths/minute. There was no murmur in the heart sound, although tachycardia was detected. The chest auscultation revealed fine crepitations on the right side more than the left side. Abdomen and extremities were normal. Laboratory investigations on the first admitted day have been presented in Table 1. The chest radiographs from the district hospital (two days before admittance) and on the day of admittance at Petchabun Hospital showed patchy infiltration of the right lower lobe (Fig 1) and patchy infiltration of the right lung with minimal pleural effusion and infiltration of the left-upper lung field (Fig 2a), respectively. Pneumonia with acute respiratory distress syndrome (ARDS) was documented and avian influenza A (H5N1) infection was suspected. Rapid test (throat swab) for influenza A was positive. Treatment consisted of intravenous fluid therapy, broad-spectrum antibiotics, neuraminidase inhibitor (oseltamivir), mechanical ventilation (volume-controlled, Bennett-7200) and other supportive treatments. Steroids were not used. High fever (38.5ºC - 40.2ºC) persisted for three days and defervesced on the fourth day. Multiple episodes of watery diarrhea developed on Day 2

Table 1
Laboratory investigations of the patient.

Date	Laboratory investigations
Sep 30, 2004	CBC : Hct 36%, WBC 2,400, Platelets 146,000, N 70%, L 25%, M 5%
	ESR : 22 mm/h ; UA: no protein, WBC, RBC; BUN/Cr : 8/0.9 mg/dl
	Electrolytes : Na^+ 137 K^+ 3.67, Cl^- 109, TCO_2^- 24 mEq/l
	Liver enzymes : AST/ALT 230/120 units/l
Oct 1, 2004	Stool examination : soft/yellow, no WBC, RBC parasite
Oct 3, 2004	CBC : Hct 35%, WBC 9,700, Platelets 131,000, N 80%, L 10%, M10%
	Electrolytes : Na^+ 140, K^+ 3.10, Cl^- 118, TCO_2^- 22 mEq/l
	Liver enzymes : AST 637, ALT 775 units/l; BUN/Cr 13/0.8 mg/dl
	LDH : 9,680 (266-500); CPK : 8,760 (0-190) units/l
	Hemoculture, stool culture, throat swab culture : no growth

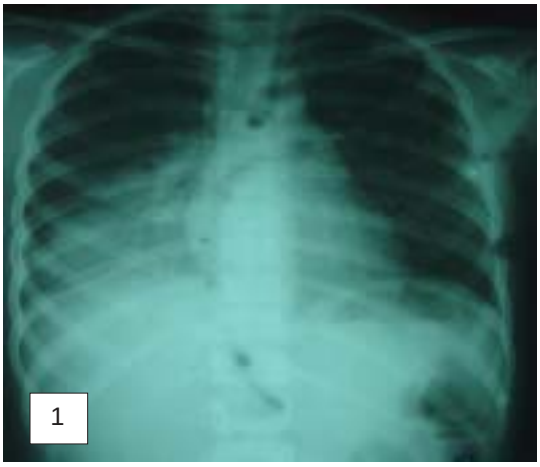

Fig 1–chest radiograph of the patient at district hospital 2 days before admission.

and 3. Worsening respiration was confirmed by serial chest radiographs (Fig 2b, 2c and 2d). Gross hematuria was noted on the fourth day. All vital signs were under controlled for only three days before becoming unstable and expiring on the fourth day. Premortal laboratory investigation on the fourth day were also presented in Table 1. Throat swab specimens were sent to the Department of Medical Science, Ministry of Public Health on the second day. Genetic materials of avian influenza A (H5N1) were detected by reverse transcriptase - polymerase chain reaction (RT-PCR) and reported two days after death. Viral culture for avian influenza A (H5N1) was also present.

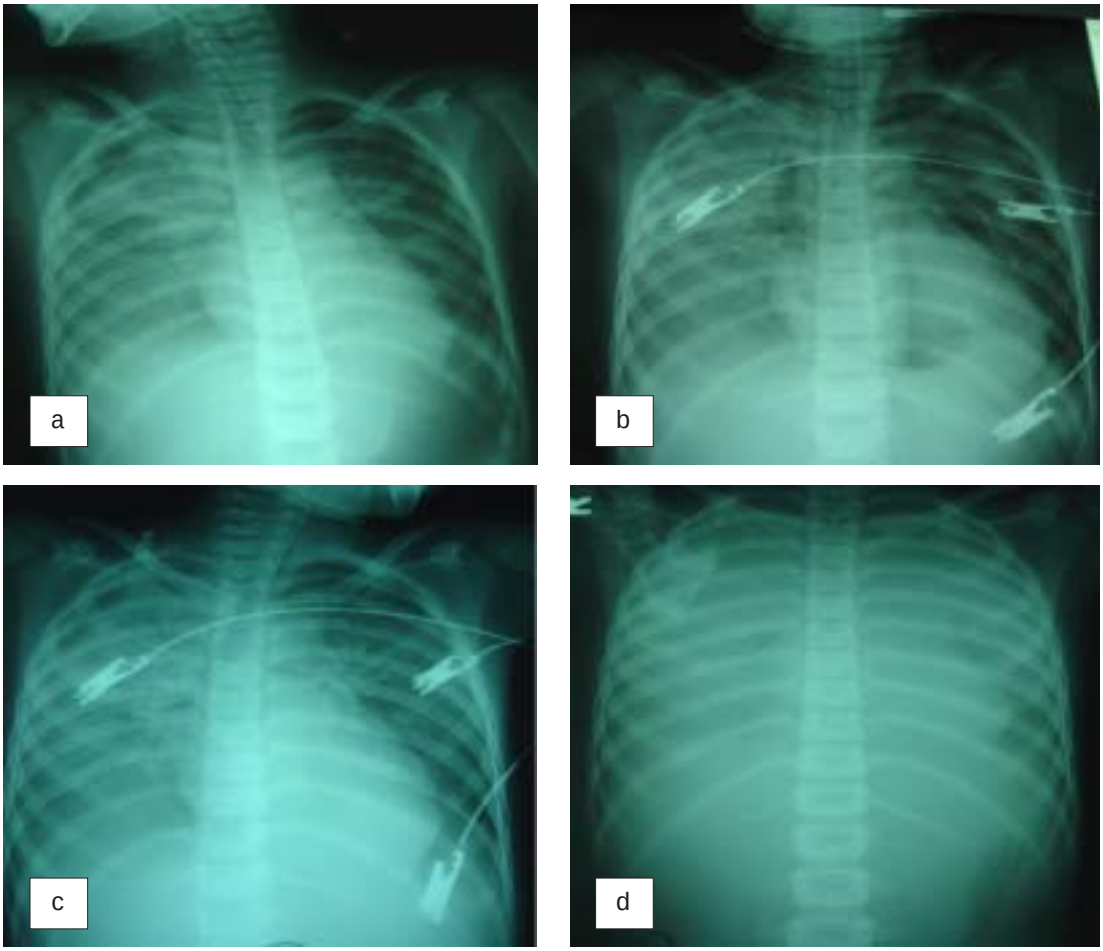

Fig 2a, 2b, 2c and 2d–chest radiographs on the first, second, third and fourth day at Petchabun Hospital, respectively.

DISCUSSION

This patient was one of five cases (four deaths) of avian influenza A (H5N1) infection documented in late 2004, the second episode of epidemic in Thailand (WHO, 2005a). The patient presented severe dyspnea, a history of close contact with ill and dead poultry documented with avian influenza A (H5N1) infection. Avian influenza A (H5N1) infection was therefore highly suspected. Although human-to-human transmission was not directly documented, it may nevertheless have occurred through close physical contact with H5N1-infected patients (Katz *et al*, 1999; Bridges *et al*, 2000; Ungchusak *et al*, 2005). She was therefore treated in a special isolation zone for air-borne transmission disease. Rapid diagnosis for influenza A was positive in the second test. It was useful with respect to the commencement of early antiviral therapy (Chotpitayasunondh *et al*, 2005), which included the use of appropriate isolation precautions and the effective investigation of contacts (Chan, 2002). A neuraminidase inhibitor (oseltamivir) was used but too late to be effective due to the severity of the initial symptoms (Chotpitayasunondh *et al*, 2005). Since the incubation period of the disease was about two to four days (Hien *et al*, 2004), her respiratory illness since three weeks before admission may have been the only aggravating factor for avian influenza A (H5N1) infection. The patients in the 2004 outbreak, which included this patient, were mainly older children (CDC, 2004a,b), whereas the 1997 outbreak mainly targeted young children and adults (Chan, 2002). Almost all patients with ARDS died (8 from 10, Hien *et al*, 2004) and 8 from 9 (Chotpitayasunondh *et al*, 2005)). A more rapid initiation of ventilatory support following a timely recognization of the disease would have led to a higher chance of survival as survived patients in the 2004 outbreak (Grose and Chokepaibulkit, 2004).

Multiple episodes of watery diarrhea were noted on Day 2 and 3 without evidence of bacterial pathogen. The first five patients with avian influenza A (H5N1) in Thailand did not have diarrhea (CDC, 2004a). There were 17, 70 and 50% of patients with diarrhea in the outbreak in Hong Kong 1997 (Chan, 2002), Vietnam 2004 (Hien *et al*, 2004), and Thailand 2004 (Chotpitayasunondh *et al*, 2005), respectively. Infections of the gastrointestinal tract by avian influenza viruses, including H5N1, was common in avian species (Webster *et al*, 1978; Shortridges *et al*, 1998), but rarely do human influenza (H1, H3) viruses infect human in the same way (Zinserling *et al*, 1983). Avian influenza A (H5N1) infection in humans presenting diarrhea without respiratory symptoms (Apisarnthanarak *et al*, 2004) and diarrhea with encephalitis (de Jong *et al*, 2005) were reported. The infection of the central nervous system by the virus was relatively common in tigers, implying that these viruses had highly pathogenic extrapulmonary manifestations (Kaewcharoen *et al*, 2004; Thanawongnuwech *et al*, 2005). Leukopenia, lymphopenia, thrombocytopenia (<150,000 cells/mm^3) (Behrman *et al*, 2000) and liver dysfunctions were detected at admission, and LDH, CPK were also relatively high. These findings when combined with ARDS and delayed hospitalization, were associated with fatal outcomes (Yuen *et al*, 1998). Maturation arrest (Chokepaibulkit *et al*, 2005), reactive histiocytosis, and hemophagocytosis (Yuen *et al*, 1998; Chan, 2002; Chokepaibulkit *et al*, 2005) are likely responsible for hematologic abnormalities. Hemophagocytosis supported the cytokine dysregulation model of the pathogenesis of severe H5N1 diseases (To *et al*, 2001; Cheung *et al*, 2002; Peiris *et al*, 2004). Detection of the H5N1 virus in human from upper respiratory specimens such as throat swabs or nasopharyngeal swabs were difficult (Yuen *et al*, 1998) since viral replication sites in human were in the lungs (mainly lower part especially type II

pneumocytes) and the gastrointestinal tract (even in the absence of diarrhea) (Uiprasertkul *et al*, 2005). However, the viral culture and genetic material of influenza A (H5N1) extracted via RT-PCR from the patient were derived from throat swab specimens. This may have been possible as a consequence of the heavy infection by the virus from prolonged close contact with infected poultry. Steroid were not used on this patient because evidence supporting a positive outcome was insufficient (Hien *et al*, 2004; Chotpitayasunondh *et al*, 2005). The causes of this patient's death should be stated as respiratory and cardiac failure with multiple organs involvement (hematologic, gastrointestinal, hepatic and renal). Although the human H5N1 viruses identified in Asia in 2004 were genetically and antigenically distinguishable from the 1997 and February 2003 (Li *et al,* 2004; CDC, 2004a), the clinical manifestations were relatively similar except for more prominent diarrhea and mortality in the former rather than the latter.

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