

Letter to the Editor

## Ratio of CD4<sup>+</sup> to CD8<sup>+</sup> T-Cells in the Recent Reported Cases of Bird Flu Infection in Asia

Viroj Wiwanitkit

Department of Laboratory Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand 10330. e-mail: wviroj@yahoo.com

### TO THE EDITOR

Influenza is an infectious disease caused by a constantly varying RNA virus. Influenza A virus is a naturally occurring infection in different animals including humans, pigs, horses, sea mammals, mustelids and birds (1). Capua and Alexander reviewed the sudden emergence of different strains of influenza A virus transmissible to humans, termed antigenic shift, which had occurred on four occasions, 1918 (H1N1), 1957 (H2N2), 1968 (H3N2) and 1977 (H1N1), each time resulting in a pandemic (1). In 1997, a new potentially devastating influenza pandemic occurred in Hong Kong, 18 cases of influenza (bird flu) caused by a novel H5N1 (chicken) influenza virus resulted in death of six individuals (2). Webster noted that separation of aquatic birds from domestic poultry in Hong Kong after the H5N1 bird flu incident could influence the interspecies transmission of influenza viruses (3).

In the year 2004, H5N1 infection reemerged in Southeast Asia. Thailand and Vietnam are the two countries endemically hit by this infection. Since January 2004, the bird flu has been detected in some poultry farms and the Thai and Vietnam governments have launched several attempts to control the infection (1, 4). During the outbreak, there were some reports of human infection causing severe disease with high mortality rate reported from Vietnam and Thailand (1, 4). Most infected patients developed progressive pneumonia with progressing and acute respiratory distress syndrome (ARDS) and died subsequently (1, 4).

Some hematologic abnormalities were noted in patients with bird flu, the main one of which was lymphopenia with decreased lymphocyte neutrophil ratio (5). Anemia was also observed in this infection (6). However, the immunohematological aspect of this viral infection has not been well documented. Here, we performed this mini-study in order to document the impact of bird flu infection on CD4<sup>+</sup>/CD8<sup>+</sup> ratio, a marker of immune depletion, as reported for patients in Thailand and Vietnam. We hypothesized that the change in CD4<sup>+</sup> and CD8<sup>+</sup> cell counts in patients infected with H5N1 strain might be similar to general influenza infection (7).

This study was designed as a descriptive retrospective analysis. A literature review on papers concerning human bird flu in Thailand was performed. The author performed the literature review on human bird flu infection reported in Thailand from database of the published works cited in the Index Medicus and Science Citation Index using key words "bird flu", "avian flu", "avian influenza" as well as "H5N1". The author also reviewed the published works in all 256 local Thai journals, which is not included in the international citation index, for the report of human bird flu infection using similar key words. The reports that contained no complete data on CD4<sup>+</sup> and CD8<sup>+</sup> counts were excluded for further analysis. Of CD4<sup>+</sup> to CD8<sup>+</sup> ratios in all reports were summarized. All the statistical analyses in this study were made using SPSS 7.0 for Windows Program.

According to this report, there were 7 reports, covering 22 Thai and Vietnamese patients with a documented diagnosis of bird flu (80–13). Five out of 22 cases had complete data on CD4<sup>+</sup> count, which were recruited for further analysis. The reported CD4<sup>+</sup>/CD8<sup>+</sup> ratios ranged from 0.59 to 1.08 with a mean value equal to  $0.75 \pm 0.20$  (median = 0.71).

Bird flu or avian flu, caused by H5N1 strain of influenza virus, is a new emerging infectious disease. Worldwide, there is an outbreak of avian flu affecting the poultry industry since 1997. Increased number of scientific data available on the molecular aspects and pathogenicity of influenza virus has generated concerns, particularly for legislative purposes and international trading (1). Kida reported that recent outbreaks of highly pathogenic avian influenza in chicken and ducks that occurred in 9 Asian countries, give us an alarm to realize that bird flu is not restricted to borders and also raised great concern towards human health as well as agricultural products (4). Kida also noted that H5N1 influenza virus has the ability to jump between species by genetic shift, with the possibility to cause severe disease with high mortality rates in humans (4).

Katz et al. concluded that in addition to high mortality rates, highly pathogenic H5N1 strains exhibit additional features that include rapid and uncontrolled replication in lungs of infected mice, dissemination and replication of virus in various organs, and depletion of peripheral blood leukocytes (13). As to leukocyte abnormality in bird flu infection, Tran et al. reported 10 cases of bird flu infection in Vietnam, in whom clinically significant lymphopenia was recorded (average lymphocyte count, 700 cells/mL) (14). This supports the suppressive effects of H5N1 strain on lymphocyte changes, explained by Katz et al (13).

Role of CD4 lymphocytes in protection against Influenza infection had been noticed previously (7). Jameson et al. noted that human CD8<sup>+</sup> and CD4<sup>+</sup> T lymphocytes are capable of recognizing specific epitopes on influenza A virus strains derived from avian species, including the H5N1 strains and this could provide partial protection to humans against novel influenza A virus strains introduced into humans from other species (15). According to our analysis, no decrease in CD4<sup>+</sup>/CD8<sup>+</sup> ratio among patients with bird flu was detected, implying that CD4<sup>+</sup> helper T cells have probably no role in conduction of immune suppression in bird flu. This finding is consistent with findings of Lewis et al. indicating that the lymphopenia seen in acute influenza infection is due to a reduction in both T and B cells without an alteration in CD4:CD8 ratio (16).

## REFERENCES

- 1 Capua I, Alexander DJ. Avian influenza and human health. *Acta Trop.* 2002; 83:1-6.
- 2 Lin YP, Shaw M, Gregory V, Cameron K, Lim W, Klimov A et al. Avian-to-human transmission of H9N2 subtype influenza A viruses: relationship between H9N2 and H5N1 human isolates. *Proc Natl Acad Sci U S A.* 2000 15; 97: 9654-8.
- 3 Webster RG. The importance of animal influenza for human disease. *Vaccine* 2002;20 :16-20.
- 4 Kida H. Avian influenza virus. *Uirusu.*2004; 54:93-6.
- 5 Wiwanitkit V. Lymphocyte - Neutrophil ratios in the recent reported cases of bird flu infection in Thailand and Vietnam. *Internet J Third World .*2005;2: 2.
- 6 Wiwanitkit V. Anemia in the recent reported cases of bird flu infection in Thailand and Vietnam. *J Infect.* 2005; 51:259.
- 7 Brown DM, Roman E, Swain SL. CD4 T cell responses to influenza infection. *Semin Immunol* 2004;16:171-7
- 8 Grose C, Chokephaibulkit K. Avian influenza virus infection of children in Vietnam and Thailand. *Pediatr Infect Dis J* 2004; 23:793-4.
- 9 Cases of influenza A (H5N1)--Thailand, 2004. Centers for Disease Control and Prevention (CDC). *MMWR Morb Mor tal Wkly Rep.* 2004 Feb 13;53:100-3.
- 10 Chotpitayasunondh T, Lochindarat S, Srisan P. Preliminary clinical description of influenza A (H5N1) in Thailand. *W Epidemiol Surveil Rep* 2004; 35: 89-92.
- 11 Chokephaibulkit K, Uiprasertkul M, Puthavathana P, Chearskul P, Auewarakul P, Dowell SF et al. A child with avian influenza A (H5N1) infection. *Pediatr Infect Dis J .*2005; 24: 162-6.
- 12 Apisarnthanarak A, Kitphati R, Thongphubeth K, Patoomanunt P, Anthanont P, Auwanit W et al . Atypical avian influenza (H5N1). *Emerg Infect Dis.* 2004; 10:1321-4.
- 13 Katz JM, Lu X, Frace AM, Morken T, Zaki SR, Tumpey TM. Pathogenesis of and immunity to avian influenza A H5 viruses. *Biomed Pharmacother* 2000;54:178-87.
- 14 patients in 10in (1N5H)Avian influenza A .Nguyen VC et al ,Pham PM ,Luong TS ,Nguyen TD ,Nguyen TL ,Tran TH .*N Engl J Med .*Vietnam2004 18;350:1179-88.
- 15 Jameson J, Cruz J, Terajima M, Ennis FA. Human CD8+ and CD4+ T lymphocyte memory to influenza A viruses of swine and avian species. *J Immunol.*1999;162:7578-83.
- 16 Lewis DE, Gilbert BE, Knight V. Influenza virus infection induces functional alterations in peripheral blood lymphocytes. *J Immunol.* 1986; 137:3777- 81.