Clinical deterioration in community acquired infections associated with lymphocyte upsurge in immunocompetent hosts

VINCENT C.C. CHENG[1], ALAN K.L. WU[2], IVAN F.N. HUNG[1], BONE S.F. TANG[1], RODNEY A. LEE[1], SUSANNA K.P. LAU[1], PATRICK C.Y. WOO[1], KWOK-YUNG YUEN[1]

From the [1]Division of Infectious Diseases, Centre of Infection, Queen Mary Hospital, The University of Hong Kong; Hong Kong Special Administrative Region, China and the [2]Division of Infectious Diseases, Department of Medicine and Therapeutics, Prince of Wales Hospital, Hong Kong Special Administrative Region, China.

K.Y.Yuen, Division of Infectious Diseases, Centre of Infection, Queen Mary Hospital, The University of Hong Kong, Hong Kong Special Administrative Region, China (Tel: +852-28554892, Fax: +852-28551241, E-mail: kyyuen@hkucc.hku.hk)

ABSTRACT

Clinical deterioration during the course of community-acquired infections can occur as a result of an exaggerated immune response of the host towards the inciting pathogens, leading to immune-mediated tissue damage. Whether a surge in the peripheral lymphocyte count can be used as a surrogate marker indicating the onset of immunopathological tissue damage is not known. In this study, we reported the clinical presentations and outcomes of a cohort of immunocompetent patients with non-tuberculous community acquired infections who experienced clinical deteriorations during hospital stay (N=85). 12 (14.1%) patients had a surge in lymphocyte count preceding their clinical deteriorations, and their diagnoses included viral pneumonitis (4), viral encephalitis (3), scrub typhus (2), leptospirosis (1), brucellosis (1), and dengue hemorrhagic fever (1). The clinical manifestations during deterioration ranged from interstitial pneumonitis (6), airway obstruction (1), CNS disturbances (4), and systemic capillary leak syndrome (1), all of which were thought to represent immunopathological tissue damages. When compared with patients without lymphocyte surge, these patients were more likely to be infected with fastidious / viral pathogens (0 vs 12; $p < 0.05$), in addition to having lower mean baseline lymphocyte counts (403 ± 181 vs 1143 ± 686 cells/μL; $p < 0.05$). We postulate that the peripheral lymphocyte count may be a useful surrogate marker indicating the presence of immunopathological damage during clinical deterioration in certain infectious diseases.

INTRODUCTION

The outcome of clinical infectious diseases depends on both the virulence of the microbes and the appropriateness of host immune responses. An intact innate immunity with or without subsequent adaptive immunity towards the infecting organisms remains the most important factor in eradicating or controlling the infections. However, clinical deterioration as a result of immunopathological damage may occur as a result of an overwhelming rebound of the immune system, either temporally related to the withdrawal of immunosuppressive therapy such as steroid or cytotoxic agents, or secondary to treatment of microbes with potent immunosuppressive effects on the host such as HIV. It is manifested as immunorestitution disease, which has been described in previous studies [1,2,3]. In addition, immune-mediated tissue damage can also develop in either immunosuppressed or immunocompetent patients infected with Mycobacterium tuberculosis, with disease manifestation or exacerbation during anti-tuberculosis therapy, a phenomenon that has been given the term 'paradoxical response' [4-9]. Recent studies showed that an upsurge of the absolute lymphocyte counts and conversion of tuberculin skin test from negative to positive occurred during paradoxical deterioration [10,11], even for patients co-infected with HIV [7]. A low baseline lymphocyte count with a subsequent greater upsurge is one of the risk factors for development of a paradoxical response [5].

Apart from tuberculosis, clinical deterioration during the course of illness can also occur in immunocompetent patients affected by certain infectious diseases, giving rise to so-called biphasic illness patterns. For instance, leptospirosis is characterized by an initial

bacteremic phase lasting 4 to 7 days, may be followed by an immune-mediated meningitis, uveitis, and pneumonitis, causing multiple organ failure [12,13]. Dengue virus infection may also present with ‘saddleback' biphasic fever pattern, followed by increased vascular permeability which can result in hypovolemic shock in some cases [14]. However, the association of an upsurge of absolute lymphocyte count with clinical deterioration in these patients has not been reported.

In this article, we report a cohort of immunocompetent patients with non-tuberculous community acquired infections in whom clinical deterioration occurred during an upsurge of the absolute lymphocyte count. The clinical spectrum of this phenomenon and its possible mechanisms are discussed.

MATERIALS AND METHODS

Patients

All clinical data were collected prospectively over a 24-month period (January 2000 – December 2001) on patients referred for infectious disease (ID) consultation in a tertiary hospital (Queen Mary Hospital, Hong Kong, a 1,350-bed teaching hospital).

Definition of clinical deterioration involving upsurge of lymphocyte count

For the purpose of this study, clinical deterioration involving upsurge of the lymphocyte count was defined as an acute symptomatic deterioration of a (presumably) pre-existing infection, which is temporally related to an increase in the absolute lymphocyte count. The acute symptomatic deterioration included worsening of neurological symptoms such as mental confusion, disorientation, and convulsions; worsening of respiratory symptoms such as respiratory distress and development of pulmonary infiltrates and pleural effusion; and hypotension with multiple organ failure.

Surge in absolute lymphocyte count was defined as rise of lymphocyte count of ≥ 500 cells / μL if the baseline lymphocyte count was less than 500 cells / μL, or double the baseline value when the lymphocyte count was more than 500 cells / μL, within a 2-day period.

Exclusion criteria

Patients receiving immunosuppressive therapy (systemic steroids, cytotoxic agents, a combination of steroid and cytotoxic agents, or irradiation) or known to have immunodeficiency or infected with HIV were excluded from this study as these

conditions may suppress the absolute lymphocyte count. Patients with chronic diseases such as diabetes mellitus, chronic renal failure, and chronic liver disease were also excluded from this study as they may have abnormal lymphocyte function. Patients with nosocomial infections were excluded because in-patient interventions may result in changes in lymphocyte count. Patients with diagnosis of M. tuberculosis infections were also excluded as they were analyzed separately in the context of paradoxical response [4,5,10]

Time to development of clinical deterioration involving upsurge of lymphocyte count

The time to development of clinical deterioration involving upsurge of lymphocyte counts was defined as the interval between the initial clinical symptoms and the onset of symptomatic deterioration as defined above.

The consultation procedure has been described previously [15,16]. Briefly, detailed history taking, physical examination and review of case notes were performed for each patient. Serial lymphocyte counts with subsequent surges, and the occurrence of symptomatic clinical deteriorations, were recorded and monitored for each patient.

Statistical evaluation

The characteristics of patients with or without lymphocyte surge during clinical deterioration were compared. The chi-square test was used for categorical variables. Continuous variables were tested by the Student's *t* test. A P value of < 0.05 was considered significant. A statistical package (SPSS 10.0; SPSS Hong Kong, Hong Kong) was used for all analyses.

RESULTS

During the 24-month period, there were 3518 inpatient ID consultations, of which 357 (10.1%) patients with median age of 59, range 2-98, were immunocompetent patients with clinical and microbiological evidence of non-tuberculous community acquired infections. Eighty-five patients had clinical deterioration during follow up (table 1). Of these 85 patients, 12 (14.1%) had an upsurge of lymphocyte count during clinical deterioration (table 2). Eight were male and four were female, with median age of 35, range 17-75. Diagnoses in these patients included viral pneumonitis (4), viral encephalitis (3), scrub typhus (2), leptospirosis (1), brucelllosis (1), and dengue hemorrhagic fever (1) (table 2). The median duration between the onset of symptoms to diagnosis was 6 days (8 days for bacterial infections and 2.5 days for viral infections). The median time of clinical deterioration was 10 days from symptom onset. But the median 'time to clinical deterioration' was 6 days and 11.5 days for viral and bacterial infection respectively. The clinical manifestations during deterioration included acute respiratory distress syndrome as a result of interstitial pneumonitis (6), severe upper airway obstruction (1), mental confusion with or without convulsions (4), and capillary leak syndrome (1). When compared with patients without lymphocyte surge, these patients were more likely to be suffering from infection by fastidious/intracellular bacteria or virus ($p < 0.05$), in addition to having a lower baseline lymphocyte count (403 ± 181 cells / μL; $p < 0.05$), a higher lymphocyte count during clinical deterioration (1813 ± 941 cells / μL; $p < 0.05$), and a greater change in lymphocyte count between baseline and clinical deterioration (1410 ± 954 cells / μL; $p < 0.05$). Although empirical antibiotics or antiviral agents were initiated in 8 (66.6%) out of 12 patients, appropriate

antibiotics or antiviral agents were given in 5 patients after the onset of clinical deterioration. One out of 12 patients died of adult respiratory distress syndrome, whereas 3 (25%) of them developed permanent functional deficits including left-sided hemiparesis, impairment of cognitive function, and chronic renal failure. The median length of stay in hospital was 24 days, range 8-269.

Case reports

Case 1

A 29 year-old man was admitted to hospital for persistent high swinging fever and headache 9 days after occupational exposure to a scrub area in Hong Kong. On admission, he had a temperature of 38.3^{o}C. Physical examination revealed conjunctival haemorrhage, diffuse maculopapular rash, hepatomegaly, and a 2 cm eschar on his right shin. Preliminary investigations showed a normal white cell count (7110 cells / μL, normal range 400-1100 cells / μL) but his lymphocyte count was depressed (370 cells / μL, normal range 150-400 cells / μL). The platelet count was low (47 x 10^9 /L, normal range 150-400 x 10^9 /L). Liver function tests showed elevated alanine and aspartate aminotransferase (ALT) 311 U/L (normal range 6-53 U/L) and aspartate aminotransferase levels and renal function was well. The chest radiograph showed pulmonary congestion. A clinical diagnosis of Rickettsial infection was made and he was given doxycycline 100 mg bd. However, he deteriorated rapidly with progressive liver impairment, renal impairment and respiratory distress, and required mechanical ventilation in intensive care unit 3 days after admission. Repeated chest radiographs demonstrated acute pulmonary edema. The hemoglobin dropped from 15.4 g/dL to 12.7

g/dL over 3 days and the platelet count further decreased to 36 x 10^9 /L. A sudden upsurge of lymphocyte count (2670 cells / μL) was observed at the time of deterioration, which further increased to 3250 cells / μL. The clinical features were compatible with endothelitis, capillary leak syndrome and multiple organ failure as a result of immunopathological damage due to severe rickettsial infection. After receiving antibiotics and methylprednisolone, he gradually recovered. His lymphocyte count decreased to 1200 cells / μL on the day of extubation. He had positive Orientia tustusgamushi IgM serology by immunofluoresence and the Weil-Felix OXK component demonstrated a four-fold rise in titre from 1:80 to 1:320 over a 2-week interval.

Case 2

A 27-year-old man presented with fever, chills, and abdominal discomfort 7 days after occupational exposure to a scrub area in Hong Kong. On admission, he was alert but had a temperature of 38^{o}C. Physical examination showed maculopapular rash, hepatomegaly, and a 1 cm eschar in his right groin. Preliminary investigations revealed a total white cell count of 5600 cells / μL with lymphopenia (300 cells / μL). The platelet count was low (27 x 10^9 /L). Liver function tests were deranged whereas renal function tests were normal. A clinical diagnosis of Rickettsial infection was made and he was given doxycycline 100 mg bd. However he deteriorated rapidly with respiratory distress, and required mechanical ventilation in the intensive care unit for 3 days after admission. A chest radiograph demonstrated acute pulmonary edema. On the day of deterioration, there was a sudden upsurge of lymphocyte (3700 cells / μL), which further increased to 3900 cells / μL one day later. The clinical features were compatible with endothelitis and capillary leak as a result of immunopathological damage secondary to severe

rickettsial infection. He was given intravenous minocycline 100 mg q12h and levofloxacin 500 mg q24h. He subsequently improved and was extubated after 5 days of mechanical ventilation. The lymphocyte count decreased to 1500 cells / μL on the day of extubation. He had positive Orientia tustusgamushi IgM serology and the Weil-Felix OXK component demonstrated a three fold serial elevation from 1:20 to 1:160 over a 2-week interval. He had a full recovery after a 4-week course of doxycycline 100 mg bd.

Case 3

A 39-year-old man presented with fever, generalized malaise, bilateral calf pain, and abdominal discomfort 6 days after a heavy rainstorm with flooding in the city. On admission, he had conjuctival suffusion and hepatomegaly. Investigations showed a normal white cell count (8700 cells / μL), but the lymphocyte count was decreased (400 cells / μL). His platelet count was 35 x 10^9 /L. The liver function was mildly elevated. The renal function tests were normal. A clinical diagnosis of leptospirosis was made and he was given intravenous penicillin 1 MU q6h. Fever subsided after 3 days of therapy. On day 5, however, he rapidly deteriorated with recurrent fever, hypotension and deranged liver and renal function. A chest radiograph revealed bilateral pulmonary infiltrates. A sudden surge in the lymphocyte count from 400 to 1100 cells / μL was observed on the day of deterioration. He was continued with intravenous penicillin for 1 week and recovered after a 2-month convalescent period. IgM antibodies to Leptospria interrogans were demonstrated by enzyme-linked immunosorbent assay.

Case 4

A 72-year-old lady with a history of dementia presented with low-grade fever, poor appetite, malaise, and generalized bone pain for 2 weeks. On admission, she was found

to have pancytopenia with hemoglobin of 7.5 g/dL, a total white cell count of 3100 cells / μL (lymphocyte of 300 cells / μL), and a platelet count of 48 x 10^9 /L. Hematological malignancy was suspected but bone marrow examination was unremarkable. On day 8, while her lymphocyte count surged to 1200 cells / μL, she became mentally confused, and disorientated in time, place, and person. Lumbar puncture was not performed because of thrombocytopenia. She was given intravenous cefoperzone-sulbactam 1 gm q8h as empirical therapy but fever persisted. Serological evidence of brucellosis was obtained by serum agglutination test, in which there was a 4-fold rise in BM from 1:20 to 1:320 over a 10-day interval. Magnetic resonance imaging of brain revealed diffuse ischemia in brainstem and thalamus. She was treated as neurobrucellosis with doxycycline 100 mg bd and rifampicin 600 mg qd for 6 months. Both her mental state and pancytopenia recovered with therapy. She probably acquired the infection by ingestion of raw meat because of inadequate cooking.

Case 5

A 33-year-old man presented with fever, chills, headache, sore throat, cough and myalgia 7 days after returning from Bangladesh. Physical examination revealed a fine diffuse macular rash over the body. On admission, he had a normal white cell count (8400 cells / μL) but had lymphopenia (400 cells / μL). His platelet count was 168 x 10^9 /L and the liver and renal function tests were normal. A clinical diagnosis of dengue fever was made. However, he had a progressive drop in platelet count (25 x 10^9 /L) and blood pressure after 3 days of admission. A chest radiograph revealed bilateral pleural effusions. A surge of the lymphocyte count (2100 cells / μL) was observed on the day of deterioration. The liver function tests were also deranged when assayed 3 days after the

upsurge of lymphocytes. He gradually improved and pleural effusion resolved after 1 month. Paired serum demonstrated a rising titer from < 10 to 1:2560 towards dengue type 2 over a 4-day interval. The dengue PCR on his acute serum was also positive.

Case 6

A 75-year-old man presented with painful reactivation of varicella zoster in the dermatomal distribution of L1. On admission, he was conscious and afebrile. The white cell count was normal (4100 cells / μL), but the lymphocyte count was low (700 cells / μL). He was given oral famciclovir 500 mg tds and the skin lesions gradually subsided. However, after 10 days of therapy, he developed generalized malaise, mental confusion, and convulsions, suggestive of encephalitis. The lymphocyte count increased to (1600 cells / μL) on the day of deterioration. Cerebrospinal fluid (CSF) revealed lymphocytic pleocytosis with a total cell count of 293 cells / μL and a lymphocyte count of 201 cells / μL. His CSF was polymerase chain reaction (PCR) positive for varicella zoster virus but a viral culture of CSF was negative. He gradually improved with intravenous acyclovir 500 mg q8h for 14 days.

Case 7

A 27-year-old man presented with neck pain, neck stiffness, and progressive headache for 1 week. On admission, he had a temperature of 37.6 ^{o}C. The white cell count and lymphocyte count were 5610 and 760 cells / μL respectively. Lumbar puncture revealed a total cell count of 819 and a lymphocyte count of 606 cells / μL. He was treated with intravenous acyclovir 500 mg ivi q8h. On day 3, he developed mental confusion with a surge in peripheral lymphocyte count to 2000 cells / μL. Anti-tuberculous therapy was started in view of the clinical deterioration. He gradually improved neurologically after 1

weeks of acyclovir and 4 days of anti-tuberculous treatment. CSF was PCR positive for HSV and for mycobacteria. Anti-tuberculous drugs were withheld and he fully recovered after 21 days of acyclovir.

Case 8

A 35-year-old woman presented with a 3-day history of fever, headache, nausea, and vomiting. On admission, she was mentally alert. Physical examination was unremarkable except for a low-grade fever of 37.8 ^{o}C. Her white cell count was normal (6200 cells / μL) and the lymphocyte count was low (500 cells / μL). On day 3, she developed mental confusion with auditory hallucination and convulsion. Computerized tomography of brain revealed a 3 cm hypodense lesion in the right temporal area. Magnetic resonance scanning showed an abnormal right temporal lobe with mild hypointense signal on T-1 weighted image and a heterogeneous hyperintense signal on T-2 weighted image, consistent with encephalitis. CSF showed a total cell count of 130 cells / μL and lymphocyte of 125 cells / μL. Her blood lymphocyte count increased from 500 to 1400 cells / μL on the day of deterioration. She was treated with intravenous acyclovir 500 mg q8h for 21 days and recovered with a residual deficit in abstract thinking. The CSF was HSV-1 PCR positive.

Case 9

A 71-year-old woman was admitted for a 2-day history of sore throat and nonproductive cough. On admission, the white cell and lymphocyte counts were 2900 and 300 cells / μL respectively. She was treated conservatively as community acquired viral infection. However, two days after admission, she deteriorated with respiratory distress and inspiratory stridor requiring mechanical ventilation. Her lymphocyte count surged from

300 to 800 cells / μL at the time of deterioration. Bronchoscopic examination showed swollen vocal cords and subglottic edema. A nasopharyngeal aspirate for direct antigen detection was positive for parainfluenza virus type 3. She required prolonged ventilation for 28 days and finally recovered on day 35.

Case 10

A 17-year-old female with mental retardation presented with flu-like symptoms for 2 days. On admission, her white cell count was normal (5600 cells / μL), with a depressed lymphocyte count (300 cells / μL). A chest radiograph was unremarkable. On day 3, she developed progressive respiratory distress and required mechanical ventilation. The chest radiograph showed bilateral interstitial opacities suggestive of pneumonitis. At the time of deterioration, her lymphocyte count increased from 1300 (day 3) to 3180 cells / μL (day 5). A nasopharyngeal aspirates showed influenza A virus by direct antigen detection. She succumbed on day 10 from adult respiratory distress syndrome despite therapy with amantidine and intravenous cefotaxime.

Case 11

A 67-year-old man with a history of chronic obstructive airway disease (COAD) was admitted complaining of shortness of breath for 2 days. On admission, his lymphocyte count was 400 cells / μL and the chest radiograph showed hyperinflated lung fields. He was diagnosed as having an exacerbation of COAD, and treatment with bronchodilators. Three days after admission he developed worsening respiratory distress, and a chest radiograph revealed interstitial pneumonitis. This was associated with a surge in the lymphocyte count of 1100 cells / μL. He was intubated and mechanically ventilated in the intensive care unit. A nasopharyneal aspirate was positive for influenza A virus by

direct antigen detection. He was extubated on day 7 and transferred to a convalescent hospital for further management.

Case 12

A 64-year-old man with an underlying history of chronic obstructive airway disease was admitted to hospital for increasing shortness of breath for 1 week. On admission, he was noted to have leucocytosis (white cell count 13700 cells / μL) and lymphopenia (total lymphocyte count 100 cells / μL). He was diagnosed as having a COAD exacerbation and treated with bronchodilators. Three days after admission he deteriorated with increasing respiratory distress, and chest radiographs revealed bilateral interstitial pneumonitis. He developed progressive respiratory failure and was subsequently intubated and mechanically ventilated. The lymphocyte count surged to 900 μ/L. A nasopharyngeal aspirate was positive for respiratory syncytial virus. He gradually recovered after 8 days of ventilation.

DISCUSSION

Clinical deterioration associated with lymphocyte surge is not a rare phenomenon, especially in the context of certain infectious diseases [1-4,10]. In our experience, it constitutes 14% of immunocompetent hosts who experienced clinical deterioration during the course of community-acquired infections. In addition to the classical examples of leptospirosis and dengue virus infection in which a "biphasic" clinical pattern may occur, infections caused by fastidious/intracellular bacteria such as Orientia tsutsugamushi, Brucella species, and other commonly encountered viruses such as influenza A virus, parainfluenza virus, respiratory syncytial virus, herpes simplex virus and varicella zoster virus were also observed in our patients with clinical deterioration during the course of illness. Endothelium-rich organs such as lungs and brain were the most commonly involved systems during clinical deterioration.

It is not surprising to observe an upsurge of the lymphocyte count in patients suffering from fastidious/intracellular bacteria and viruses because an adaptive immune response is required for their clearance [17]. However, the clinical outcome of infection is dependent on the appropriateness and exactness of the development of adaptive immunity. An overwhelming and exaggerated immune response may lead to excessive immunopathological damage at the tissue level [1]. This phenomenon is exemplified by scrub typhus, caused by O. tsutsugamushi, which is a gram negative obligate intracellular bacterium transmitted by the bites of infected mite. The pathologic damage of scrub typhus included disseminated vasculitis and perivasculitis of small blood vessels as a result of direct invasion and proliferation of O. tsutsugamushi in the vascular endothelial

cells, which may lead to multiple organ failure [24]. In experimental studies, transient immunosuppression occurred during acute infection [18]. Subsequent development of specific T lymphocytic response, especially T-helper 1 cells, and development of delay-type hypersensitivity were important for protective immunity [20-23]. However, an overwhelming immune response may contribute to the development of acute respiratory distress syndrome, which is caused by interstitial infiltration of lymphocytes without any evidence of vasculitic damage [25]. However, the serial lymphocyte counts were not mentioned during clinical deterioration in these case reports.

As for viral infection, dengue hemorrhagic fever occurred as a result of massive T lymphocyte activation leading to high level of inflammatory cytokine production such as interferon γ, interleukin 2, tumor necrosis factor α. Overproduction of cytokines that affect monocytes, endothelial cells, and hepatocytes may result in capillary leakage and deranged liver function [26,27]. Development of T cell mediated immunity in respiratory virus infection has been associated with immunopathological damage in lungs in various experimental models [28,29]. Influenza infection in CD8 T-cell depleted mice presented with less significant histological evidence of inflammatory injury which suggested that host T cells played a role in the immunopathological process [30]. Further study demonstrated that antigen-specific CD8 T cells were capable of recognizing an alveolar epithelial autoantigen, which triggered an inflammatory cascade and resulted in lung damage [31]. In contrast to CD8 T cell mediated damage in influenza virus infection, CD4 T cells have been shown to be detrimental to the host by mediating immunopathological damage in respiratory syncytial virus infection [32].

It is possible that the upsurge in lymphocyte count may have been caused by specific microbial components or products. One interesting example illustrating some of the potential mechanisms may be found in the model of pertussis infection. Infection by Bordetella pertussis has been reported to result in peripheral blood lymphocytosis in infants [33,34]. The expression of L-selectin (CD62L), an important cell surface adhesion molecule mediating extravasation of blood lymphocytes into tissues and homing of lymphocytes to lymph nodes, has been found to be marked reduced in infants with pertussis infection [33,34]. In addition, it has been shown in animal models that expression of other lymphocyte adhesion molecules such as CD11a and CD18 (LFA-1) are also reduced in macaques treated with pertussis toxin [35]. The significant down-regulation of these adhesion molecules may prevent lymphocyte migration to areas of infection and homing of T and B cells to peripheral lymphoid tissues, resulting in peripheral blood lymphocytosis.

In additional to the microbial factors, specific host factors might have contributed to the upsurge in lymphocytes. Various cytokine levels can affect the lymphocyte count; for instance, increase in lymphocyte count has been shown to correlate with response to interleukin 2 therapy for malignant conditions [36,37]. Even acute stress may lead to changes in lymphocyte count as a result of changes in integrin expression and lymphocyte trafficking in the body [38]. Thus, it is possible that the cytokine response or stress induced by some of the microbes may have contributed to the lymphocyte upsurge. However, the scope of our study does not allow us to measure the various cytokine levels or to determine the pattern of expression of adhesion molecules on the lymphocytes.

Besides having lymphocyte upsurge during hospitalizations, many of our patients also had low lymphocyte counts on admission. Lymphopenia is not uncommonly observed in the acute phase of viral infections, such as during infection by respiratory syncytial virus [39], avian influenza [40] and even SARS [41]; in can also occur in the setting of severe sepsis [42]. One limitation of our study is that we could not differentiate whether the lymphocyte upsurge observed in our patients actually reflect initial migration of lymphocytes to infected tissues followed by subsequent rebound, or the effect of microbial and/or cytokine mediated lymphocyte apoptosis followed by reconstitution later in disease course. Further studies are warranted to delineate the underlying immunopathological mechanisms involved in this interesting phenomenon.

The exact mechanism mediating the immunopathology in various types of clinical infectious diseases requires further investigation. However, peripheral lymphocyte counts may act as a surrogate marker indicating the onset of possible immunopathological damage, which may be useful to infectious disease specialists who are involved in the care of these patients. Studies on lymphocyte subsets and cytokine levels would be useful in understanding this clinical entity.

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Table 1. *Characteristics of immunocompetent patients with clinical deterioration following culture-documented community acquired infection*

	Patients without upsurge of lymphocyte counts (n = 73)	Patients with upsurge of lymphocyte counts (n=12)	P value
Age (mean ± S.D.)	59.7 ± 20.0	46.3 ± 21.5	NS
Sex (male: female)	1.5: 1	2: 1	NS
Predominant infecting microbes			
Non-fastidious bacteria	73	0	< 0.05
Fastidious bacteria	0	4 *	< 0.05
Viruses	0	8 #	< 0.05
Reasons for clinical deterioration			
Primary infective complications	21	0	0.03
Nosocomial infective complications	32	0	< 0.05
Antibiotic side effects	13	0	NS
Others non infective complications	7	12	< 0.05
Acute respiratory distress syndrome	0	6	< 0.05
Upper airway obstruction	0	1	< 0.05
Mental confusion +/- convulsion	0	4	< 0.05
Capillary leak syndrome	0	1	< 0.05
Gastrointestinal bleeding	3	0	NS
Deep vein thrombosis	2	0	NS
Atrial fibrillation	1	0	NS
Accidental fracture	1	0	NS
Baseline lymphocyte count (cells/μL), mean ± S.D.	1143 ± 686	403 ± 181	< 0.05
Lymphocyte count at clinical deterioration (cells/μL), mean ± S.D.	1081 ± 539 #	1813 ± 941	< 0.05
Change in lymphocyte count between baseline and clinical deterioration (cells/μL), mean ± S.D.	335 ± 304	1410 ± 954	< 0.05

* Brucella species (1), Leptospira species (1), Orientia tsutsugamushi (2); # dengue virus (1), herpes simplex virus (2), influenza A virus (2), parainfluenza virus (1), respiratory syncytial virus (1), varicella zoster virus (1).

Table 2. *Characteristics of patients with clinical deterioration associated with upsurge of lymphocyte*

Case no.	Sex / age	Infectious diagnosis (organisms)	Lym count - baseline (cells/ μL)	Lym count - during deterior ation (cells/ μL)	Duration between onset of symptom to diagnosis	Duration between onset of symptom to deteriorati on	Antimicrobial therapy before deterioration	Clinical features during deterioration	Therapy after deterioration	Outcome & (length of stay in hospital)
1	M/29	Scrub typhus (Orientia tsutsugamushi)	370	2670	9 days	12 days	Doxycycline given 2 day before deterioration	Respiratory distress, interstitial pneumonitis requiring mechanical ventilation, acute liver and renal failure	Chloram-phenicol, minocycline, levofloxacin, methy-prednisolone	Recovered (72 days)
2	M/27	Scrub typhus (Orientia tsutsugamushi)	300	3700	7 days	10 days	Doxycycline given 2 day before deterioration	Respiratory distress, interstitial pneumonitis requiring mechanical ventilation	Doxycycline	Recovered (24 days)
3	M/39	Leptospirosis (Leptospira interrogans)	400	1100	6 days	11 days	Penicillin given 5 days before deterioration	Respiratory distress, interstitial pneumonitis, acute liver and renal failure	Penicillin	Recovered with residual renal dysfunction (17 days)
4	F/72	Brucellosis	300	1200	38 days	22 days	Cefoperazone-sulbactam 2 days before deterioration	Mental confusion, disorientation in time, place, and person	Doxycycline, rifampicin for 6 months	Recovered (269 days)
5	M/33	Dengue hemorrhage fever (Dengue virus)	400	2100	3 days	6 days	Nil	Pleural effusion, thrombocytopenia, liver dysfunction	Supportive	Recovered (8 days)

6	M/75	Varicella encephalitis (varicella-zoster virus)	700	1600	1 day	10 days	Famciclovir given 10 days before deterioration	Mental confusion & convulsion	Intravenous acyclovir	Recovered with residual lower limbs weakness (26 days)
7	M/27	Herpes simplex encephalitis (herpes simplex virus)	760	2000	7 days	10 days	Acyclovir 1 day before deterioration	Mental confusion	Intravenous acyclovir	Recovered (17 days)
8	F/35	Herpes simplex encephalitis (herpes simplex virus)	500	1400	6 days	6 days	Amoxicillin-clavulanate	Mental confusion, auditory hallucination, & convulsion	Intravenous acyclovir	Recovered with deficit in cognitive function (19 days)
9	F/71	Croup (parainfluenza virus type 3)	300	800	2 days	4 days	Nil	Severe croup with upper airway obstruction	Supportive	Recovered (32 days)
10	F/17	Viral pneumonitis (influenza A virus)	300	3180	2 days	7 days	Amoxicillin-clavulanate	Respiratory distress, interstitial pneumonitis requiring mechanical ventilation	Amantadine, supportive	Died (30 days)
11	M/70	Viral pneumonitis (influenza A virus)	400	1100	2 days	5 days	Nil	Respiratory distress, interstitial pneumonitis requiring mechanical ventilation	Supportive	Recovered (11 days)
12	M64	Viral pneumonitis (respiratory syncytial virus)	100	900	8 days	11 days	Nil	Respiratory distress, interstitial pneumonitis requiring mechanical ventilation	Supportive	Recovered (29 days)