General Internal Medicine and Clinical Innovations

Review Article

Dengue and influenza associated acute pulmonary embolism: An overview

Yee-Huang Ku[1], Wen-Chi Hsu[2] and Wen-Liang Yu[3,4*]

[1]Department of Internal Medicine, Chi Mei Medical Center-Liouying, Tainan, Taiwan

[2]Department of Nursing, Chi Mei Medical Center, Tainan, Taiwan

[3]Department of Intensive Care Medicine, Chi Mei Medical Center, Tainan, Taiwan

[4]Department of Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

Abstract

Acute pulmonary embolism (PE) often occurs in some patients with hereditary and acquired factors predisposing them at a risk for the development of thrombotic events. The hereditary hypercoagulable state due to genetic mutations involves loss of endothelium non-thrombogenic protective factors, thus linking to an increase risk of blood clots. The acquired factors are commonly seen in some infectious diseases, such as influenza, whereas dengue fever has been rarely described. Influenza and dengue are diseases of international public health importance and their differentiation of diagnosis is especially challenging because of potential overlap of both epidemic seasons in the endemic countries. The influenza A (H1N1) virus has been commonly reported to be associated with the development of acute PE. Although rare, some cases of PE occurring in acute dengue infection were reported. Little is known about whether coinfection of influenza and dengue would increasingly predispose a patient to PE during the acute phase of infections. Finally, clinicians should consider the diagnosis of influenza in appropriate seasons among patients with suspected dengue during a dengue outbreak. It is important for physicians to have a heightened awareness of both influenza and dengue at a risk for acute PE, especially in patients with increased procoagulant activity.

Introduction

Acute pulmonary embolism (PE) is a life-threatening condition and the common cause of death is due to obstruction of main pulmonary vessels by the embolus, resulting in pulmonary hypertension followed by right-sided heart failure. Acute PE is the third most common cause of mortality among the cardiovascular diseases, after coronary artery disease and stroke, accounting for 50,000 to 200,000 deaths annually [1]. The classic PE symptoms include cough, haemoptysis, pleuritic pain, acute dyspnoea or circulatory collapse. On the contrary, more cases of peripheral PEs, such as isolated sub segmental PE, have thereby been identified in the patients who may have a more benign clinical presentation compared to those with proximal PEs [1].

The 2009 pandemic influenza A (H1N1) developed as a novel swine influenza which caused more diseases among younger age groups than in the elderly. Severe hypoxemic respiratory failure from influenza A (H1N1) pneumonia resulted in an increased need for intensive care unit (ICU) beds. Pregnant women were a particularly vulnerable group of patients, who are at a higher risk for adverse outcomes. The Centres for Disease Control and Prevention (CDC) in the United States reported on the first ten patients with severe illness and acute hypoxemic respiratory failure associated with influenza A (H1N1) infection, none of whom were pregnant, but they noticed that half of the patients had a PE [2].

Dengue fever has been a major public health problem of several countries in endemic area. The main concern has been the severe forms of dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) [3]. In DHF, haemorrhagic manifestations of different degrees are common. However, thrombotic events are uncommonly reported in despite of the wide range of increased procoagulant activity during dengue fever illness [3,4]. Vascular events of deep vein thrombosis (DVT) and PE associated with acute dengue infection have been sparsely described [3,4].

Although ever reported in influenza A (H1N1) pandemics and dengue fever, the association with acute PE is still controversial. Such vascular complications could have been overlooked in the diagnosis of influenza A (H1N1) infection and dengue fever, particularly given that the major concern is the haemorrhagic event in DHF. Therefore, the purpose of this article is to provide an overview of published data and our clinical experience about the development of acute PE in patients with severe dengue and influenza infection.

Acute PE

The incidence of acute PE is increasing, which has posed a substantial financial burden to the community. There are hereditary and acquired risk factors associated with PE [5], including cellular, genetic and auto-immune factors known to play an important role in the generation of thrombi, which causes arterial and/or venous thrombosis [6]. DVT and PE are complications associated with the hypercoagulable state produced in some patients with genetic mutations, which are linked to an increase risk of blood clots. For examples, factor II gene G20210A (FII20210A), factor V Leiden (FVL, G1691A) and

Correspondence to: Wen-Liang Yu, Department of Intensive Care Medicine, Chi Mei Medical Center, Taiwan; E-mail: Yuleon_md@yahoo.com.tw

Key words: *Coinfection, Dengue, H1N1, Influenza, Pulmonary embolism*

Received: September 15, 2017; **Accepted:** October 13, 2017; **Published:** October 17, 2017

methylenetetrahydrofolate reductase gene C677T (MTHFR677T) single nucleotide polymorphisms are the most common mutations of thrombophilic diseases [7]. Antiphospholipid syndrome is a systemic autoimmune disease characterized by a persistently high titre of antiphospholipid antibodies (aPLs), of which such as anticardiolipin antibodies (aCLs) mediate the thrombotic pathophysiology. The aCLs may contribute to tissue pathology by forming immune-complexes with cardiolipin and rheumatoid factor. The thrombi formed by the induction of aPLs can lead to DVT, PE, myocardial infarction, stroke and gangrene [6].

The diagnosis of PE can be difficult because of the nonspecific symptoms. Nonetheless, the development in the diagnostic methods has reached much improvement. Evidence-based algorithms can help establish clinical probability and the severity of PE. Classic diagnostic approach of PE is a sequential combination assessment beginning with clinical assessment, radiologically unilateral hyperlucent lung, validated with D-dimer measurement, echocardiography, ventilation-perfusion lung scintigraphy and confirmed with pulmonary angiography [5]. Modern diagnostic techniques include computed tomography pulmonary angiography (CTPA) imaging and magnetic resonance angiography, which are promising approaches for diagnosis of suspected PE. For patients in the emergency department with suspected acute PE, CTPA is the test of choice for most emergency physicians [8,9].

Anticoagulant therapy is the standard treatment for PE. However, thrombolytic treatment is a significant alternative in high risk of PE as it provides rapid clot resolution [5].

Influenza infection and PE

Acute PE has been identified a major contributing cause of death in hospitalized non-surgical patients at a department of infectious diseases, particularly among those with respiratory tract infections [10]. Among them, early deaths were due to infection whereas later deaths were associated with other factors, such as PE.

Influenza is a well-known infection that may be associated with PE. A patient with primary Sjögren's syndrome developed PE following infection with influenza A virus due to synchronous development of IgM-aCLs with antibodies against influenza A two weeks after hospitalization [11]. An 11-year-old boy with familial protein S deficiency developed thrombotic microangiopathy (TMA) and PE during the acute phase of H1N1 influenza. Plasma von Willebrand factor (VWF) was elevated. Influenza-associated cytokines enhanced the release of unusually large VWF multimers from vascular endothelial cells and promoted the formation of platelet thrombi, TMA and PE [12]. Two patients with rapidly progressive hypoxemia associated with influenza A (H3N2) virus infection were diagnosed with influenza-related acute PE and were successfully treated by anticoagulant therapy [13].

However, van Wissen and colleagues reported that influenza infection was not associated with an increased risk of acute PE [14]. In their study, case patients with PE (n = 102) were compared to controls without PE (n = 395). The percentage of patients with influenza A was higher in the control group compared to the case group (4.3% versus 1.0%, respectively, odds ratio 0.22; 95% CI: 0.03-1.72). Meanwhile, influenza B was not detectable in any of the cases but was found in 3 of the 395 controls (0.8%).

Since March 2009 in Mexico, the influenza A (H1N1) pdm09 virus caused a severe outbreak in Mexico. The virus quickly spread throughout the world, leading the World Health Organization to declare a state of pandemic influenza in April 2009 (http://www.who.int.lib.chimei.org.tw:81/csr/don/2009_04_24/en/index.html). Thereafter, association of influenza infections with procoagulant changes has been recognized in most of reports in the literature. Among 14 patients with influenza A (H1N1) infection required ICU admission and advanced mechanical ventilation, 5 (36%) patients were diagnosed to have PE by CT imaging [15]. In addition, peripheral PE occurred in 5 (62.5%) of 8 patients with fatal novel influenza A (H1N1) infection [16]. Dimakakos and colleague observed an even higher incidence of PE in 6 (85.7%) of 7 influenza A (H1N1) virus infection cases [17].

Therefore, acute-onset PE should be considered in some patients with sudden, unexplained dyspnoea during an outbreak of influenza infection and prompt diagnosis is essential to save the patient from acute death associated with influenza [13]. It is reasonable to recommend that patients with severe influenza A (H1N1) pneumonia and respiratory failure should be administered DVT prophylaxis especially if there are additional risk factors for PE [2]. Besides, influenza vaccination is associated with a reduced risk of venous thromboembolism [18].

Dengue fever and PE

Dengue is a mosquito-borne viral infection caused by one of the four dengue viruses (DENV-1 to 4). Each of these viruses is capable of causing nonspecific febrile illnesses, classic dengue fever and severe dengue, including DHF and DSS [3].

There is a substantially contradictory proportion of dengue and embolism as between haemorrhagic and thrombotic events, respectively. Various factors of procoagulant activity may increase during dengue fever, including severe dehydration, increased cytokines, fibrinolysis, the complement system, plasminogen activator inhibitor-1 and disseminated intravascular coagulation, as well as low concentrations of plasma anticoagulant proteins C and S, and antithrombin III. However, these factors may contribute to microthrombi formation, but have rarely been associated with large vessel thrombosis [3]. Agarwal and colleague reported a 55-year-old man of Asian Indian ethnicity who developed large vein thrombotic event of DVT and PE in the acute phase of DHF. His condition was complicated by thrombocytopenia [4].

Five (5.4%) of 92 cases with the acute phase of dengue fever were complicated with large vein thrombotic events, according to a report in Brazil [3]. Except for 4 patients with IgM-aPLs, other known risk factors for thrombotic events were absent in these 5 patients. All thrombotic events, including DVT, PE and mesenteric vein thrombosis, were identified within the first five days of dengue illness. All 5 patients were treated with low molecular weight heparin and were recovered. Ghatak et al [19] reported spontaneous thrombosis of right internal jugular vein and subclavian vein as well as peripheral PE in a healthy female student with factor V Leiden mutation and activated protein C resistance during an acute phase of dengue infection. She was recovered after receiving intravenous heparin followed by oral anticoagulant therapy. Therefore, patients with PE and dengue could be cautiously treated with anticoagulant and/or thrombolytic regimens just as in other thrombotic disorders, if the international normalized ratio of prothrombin time is normal or slightly prolonged and no haemorrhagic events occur concurrently.

Coinfection of influenza and dengue fever

It is difficult to distinguish influenza from dengue fever among febrile illnesses in a dengue-endemic area, especially because peak dengue season often coincides with that of other common febrile illnesses in tropical regions. The influenza and dengue seasons may

overlap, which could lead to diagnostic difficulties. The first laboratory-confirmed case of coinfection with dengue and influenza A (H1N1) pdm09 strain was reported in Jeddah, Saudi Arabia [20]. Later, among 35 with suspected dengue and respiratory symptoms in El Salvador during the 2012 influenza season, 39% positive for influenza and 14% were positive for dengue. One percent presented coinfection between influenza and dengue [21]. Besides, dengue coinfection was found to increase the severity of influenza disease, though this is based on few studies of dengue [22]. Four fatal patients with laboratory-confirmed influenza A (H1N1) pdm09 and dengue virus coinfections occurred in a dengue endemic area during the dengue and influenza season [23]. Therefore, clinicians should consider the diagnosis of influenza among patients with suspected dengue to avoid fatal outcomes, especially during the influenza season in locations where these two viruses' epidemic periods coincide.

Dengue fever, influenza infection and acute PE

Acute PE has been reported in association with dengue fever or severe influenza, particularly influenza A (H1N1). Coexistence of severe dengue, influenza B and acute PE could also occur in a single patient [24,25].

In 2015, during a large dengue outbreak at Tainan city in Taiwan [24], we identified a rare coexistence of influenza B infection and pulmonary embolism after five days of hospitalization for dengue fever [25]. The patient experienced worsening dyspnoea, hypoxemia and pulmonary edema during the recovery phase of dengue fever. The blood proteins C and S had relatively lower activities, suggesting with underlying mild risk for increased thrombophilia activity [26,27]. The risk of thrombosis might not be detectably associated with mild deficiency of proteins C Ad S, but could be provoked by dual dengue fever and influenza infection.

Conclusion

The diagnosis of influenza and dengue fever coinfection could be overlooked because the clinical syndromes produced by influenza and dengue fever can be mimicked by each other. In dengue-endemic countries or during dengue outbreak period, physicians should consider the possibility of influenza and dengue coinfection earlier in the process in order to avoid late diagnosis and fatal outcomes. Acute PE could occur in the patients with influenza and/or dengue, either alone or coinfection, particularly in those patients with hereditary thrombophilia, such as factor V Leiden deficiency, antiphospholipid syndrome, as well as proteins C and S deficiency. Awareness for the vascular thrombotic complications should be recommended to all practitioners who treat patients with dengue fever, particularly coinfected with influenza. Further studies of pathogenesis are required to recognize pathogenetic link of acute PE to dengue and influenza coinfection.

Conflict of interest

None declared

Financial support

None declared

References

1. Yoo HH, Queluz TH, El Dib R (2016) Anticoagulant treatment for subsegmental pulmonary embolism. *Cochrane Database Syst Rev* 1: CD010222. [Crossref]

2. Avnon LS, Munteanu D, Smoliakov A, Jotkowitz A, Barski L (2015) Thromboembolic events in patients with severe pandemic influenza A/H1N1. *Eur J Intern Med* 26: 596-598. [Crossref]

3. da Costa PS, Ribeiro GM, Junior CS, da Costa Campos L (2012) Severe thrombotic events associated with dengue fever, Brazil. *Am J Trop Med Hyg* 87:741-742. [Crossref]

4. Agarwal A, Sharma S, Airun M (2016) Life-threatening thrombo-embolic events in a case of dengue hemorrhagic fever. *J Assoc Physicians India*; 64:87-89.

5. Duru S, KeleÅŸoÄŸlu A, ArdÄ±Ã§ S (2014) Clinical update on pulmonary embolism. *Arch Med Sci* 10: 557-565. [Crossref]

6. Islam MA, Alam F, Sasongko TH, Gan SH (2016) Antiphospholipid antibody-mediated thrombotic mechanisms in antiphospholipid syndrome: Towards pathophysiology-based treatment. *Curr Pharm Des* 22: 4451-4469.

7. Ozturk N, Baygutalp NK, Bayramoglu A, Polat H, Gul MA, et al. (2016) The evaluation of serum copeptin levels and some commonly seen thrombophilic mutation prevalence in acute pulmonary embolism. *Biochem Genet* 54: 306-312.

8. Devaraj A, Sayer C, Sheard S, Grubnic S, Nair A, et al. (2015) Diagnosing acute pulmonary embolism with computed tomography: imaging update. *J Thorac Imaging* 30: 176-192. [Crossref]

9. Ma Y, Yan S, Zhou L, Yuan DT (2016) Competitive assessments of pulmonary embolism: Noninvasiveness versus the golden standard. *Vascular* 24: 217-224.

10. Gårdlund B (1985) Fatal pulmonary embolism in hospitalized non-surgical patients. *Acta Med Scand* 218: 417-421. [Crossref]

11. Ulvestad E, Kanestrøm A, Tengnér P, Gjerde S, Sundal J, et al. (2000) Anti-cardiolipin autoantibodies and pulmonary embolism. A case for a common cause. *Scand J Rheumatol* 29: 330-333. [Crossref]

12. Tsujii N, Nogami K, Yoshizawa H, Hayakawa M, Isonishi A, et al. (2016) Influenza-associated thrombotic microangiopathy with unbalanced von Willebrand factor and a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 levels in a heterozygous protein S-deficient boy. *Pediatr Int* 58: 926-929

13. Ohrui T, Takahashi H, Ebihara S, Matsui T, Nakayama K, et al. (2000) Influenza A virus infection and pulmonary microthromboembolism. *Tohoku J Exp Med* 192: 81-86. [Crossref]

14. van Wissen M, Keller TT, Ronkes B, Gerdes VE, Zaaijer HL, et al. (2007) Influenza infection and risk of acute pulmonary embolism. *Thromb J* 5: 16. [Crossref]

15. Agarwal PP, Cinti S, Kazerooni EA (2009) Chest radiographic and CT findings in novel swine-origin influenza A (H1N1) virus (S-OIV) infection. *AJR Am J Roentgenol* 193: 1488-1493.

16. Harms PW, Schmidt LA, Smith LB, Newton DW, Pletneva MA, et al. (2010) Autopsy findings in eight patients with fatal H1N1 influenza. *Am J Clin Pathol* 134: 27-35.

17. Dimakakos E, Grapsa D, Vathiotis I, Papaspiliou A, Panagiotarakou M, et al. (2016) H1N1-induced venous thromboembolic events? results of a single-institution case series. *Open Forum Infect Dis* 3: ofw214.

18. Zhu T, Carcaillon L, Martinez I, Cambou JP, Kyndt X, et al. (2009) Association of influenza vaccination with reduced risk of venous thromboembolism. *Thromb Haemost* 102:1259-1264

19. Ghatak T, Singh RK, Baronia AK (2013) Spontaneous central vein thrombosis in a patient with activated protein C resistance and dengue infection: An association or causation? *J Anaesthesiol Clin Pharmaco* 29: 547-549.

20. Hussain R, Al-Omar I, Memish ZA (2012) The diagnostic challenge of pandemic H1N1 2009 virus in a dengue-endemic region: a case report of combined infection in Jeddah, Kingdom of Saudi Arabia. *J Infect Public Health* 5: 199-202.

21. Chacon R, Clara AW, Jara J, Armero J, Lozano C, et al. (2015) Influenza illness among case-patients hospitalized for suspected Dengue, El Salvador, 2012. *PLoS One* 10: e0140890.

22. Cohen AL, McMorrow M, Walaza S, Cohen C, Tempia S, et al. (2015) Potential impact of co-infections and co-morbidities prevalent in Africa on influenza severity and frequency: A systematic review. *PLoS One* 10: e0128580.

23. Perdigão AC, Ramalho IL, Guedes MI, Braga DN, Cavalcanti LP, et al. (2016) Coinfection with influenza A(H1N1) pdm09 and dengue virus in fatal cases. *Mem Inst Oswaldo Cruz* 111: 588-591.

24. Chen CM, Chan KS, Yu WL, Cheng KC, Chao HC, et al. (2016) The outcomes of patients with severe dengue admitted to intensive care units. *Medicine (Baltimore)* 95: e4376. [Crossref]

25. Hsu WC, Yu WL (2017) Acute Pulmonary Embolism in Dual Dengue Fever and Influenza B Infection. *Int J Virol AIDS*; 4:033.

26. Miletich J, Sherman L, Broze G Jr (1987) Absence of thrombosis in subjects with heterozygous protein C deficiency. *N Engl J Med* 317: 991-996. [Crossref]

27. Duebgen S, Kauke T, Marschall C, Giebl A, Lison S, et al. (2012) Genotype and laboratory and clinical phenotypes of protein s deficiency. *Am J Clin Pathol* 137: 178-184. [Crossref]