Open Forum Infectious Diseases

BRIEF REPORT

H1N1-Induced Venous Thromboembolic Events? Results of a Single-Institution Case Series

Evangelos Dimakakos,[1] Dimitra Grapsa,[1] Ioannis Vathiotis,[1] Aggeliki Papaspiliou,[2] Meropi Panagiotarakou,[3] Emmanouil Manolis,[4] and Konstantinos Syrigos,[1]

[1]3rd Department of Medicine, [2]9th Pulmonary Clinic, [3]6th Pulmonary Clinic, and [4]Central Respiratory Failure-Intensive Care Unit, "Sotiria" General Hospital, Medical School, University of Athens, Greece

We describe the clinical and imaging characteristics of 7 cases with polymerase chain reaction-confirmed novel influenza A H1N1 virus (pH1N1) infection who developed venous thromboembolic events (VTEs) while being hospitalized for influenza pneumonia. Pulmonary embolism (PE) without deep vein thrombosis (DVT) was observed in 6 of 7 cases (85.7%); PE with underlying DVT was found in 1 patient (14.3%).

Keywords. deep vein thrombosis; influenza; pH1N1; pulmonary embolism; venous thromboembolic events.

Novel influenza A H1N1 virus (pH1N1), which was the predominant strain globally in the 2009 pandemic, continues to circulate along with other influenza strains in the postpandemic era, and it was again the predominant serotype during the European 2015–2016 flu season [1, 2]. Risk factors for increased pH1N1-associated morbidity and mortality among infected individuals are largely similar to those described for other influenza viruses, and these factors mainly include obesity, pregnancy, immunosuppression, chronic pulmonary diseases, and other significant comorbidities, and low socioeconomical status, restricting access to medical care [1]. This new virus is nevertheless well known for its strong association with high cardiovascular mortality [3] and a high propensity to avoid the old and preferentially affect young and otherwise healthy adults, resulting in a clustering of severe and even fatal cases in patients aged between 30 and 50 years [1].

In recent years, there has been an emergence of clinical data suggesting that pH1N1 infection may also predispose patients to the development of thromboembolic complications. Previous observational and autopsy studies have documented the occurrence of both venous—often massive—and severe arterial events among patients with pH1N1 infection [4–9], but the epidemiologic association between pH1N1 and thromboembolism as well as the pathophysiologic mechanisms underlying this potential association remain to be established.

The aim of our study was to further investigate the characteristics of venous thromboembolic disease among patients with pH1N1 infection. For this purpose, we retrospectively reviewed and analyzed the clinical and imaging data of 7 patients who developed venous thromboembolic events (VTEs) while being hospitalized for pH1N1-related pneumonia.

METHODS

We conducted a retrospective chart review of patients with VTEs (pulmonary embolism [PE] and/or deep vein thrombosis [DVT]) and concomitant pH1N1 infection, treated at Sotiria Athens General Hospital, Athens, Greece, between January 2016 and April 2016. Patients included had laboratory-confirmed pH1N1 infection (by positive polymerase chain reaction [PCR] test results on nasopharyngeal swab specimens) and imaging evidence of VTEs; either PE, diagnosed with computed tomography pulmonary angiography, or DVT diagnosed with color duplex ultrasonography. Color duplex sonography of extremities was performed in all patients for the confirmation or exclusion of DVT. Hospitalized patients with presumed or suspected (but not laboratory-confirmed) pH1N1 infection, as well as those who tested negative for pH1N1 infection by PCR, were excluded from this study.

RESULTS

Seven patients with VTEs and concomitant pH1N1 infection, including 1 case of PE with underlying DVT and 6 cases of PE without underlying DVT ("de novo" PE), were identified, among a total of 44 cases of VTEs admitted to our hospital during the same time period. The latter included 11 cases of DVT, 24 cases of PE with underlying DVT, and 9 cases of de novo PE.

Mean and median age of our patients was 51 years (range, 38–73 years) and 49 years, respectively. A total of 85.7% of patients (6 of 7) were males. The demographic, clinical, and imaging characteristics of all our studied cases are presented in Table 1. The most common comorbidity in our series was arterial hypertension, seen in 3 patients, including one patient (case 4) with concurrent coronary artery disease and diabetes mellitus, a second patient (case 5) with dyslipidemia, and a third patient (case 7) with dyslipidemia and hypothyroidism.

Received 14 July 2016; editorial decision 7 October 2016; accepted 18 October 2016.

Correspondence: D. Grapsa, MD, PhD, 3rd Department of Medicine, "Sotiria" General Hospital, Medical School, University of Athens, Athens, Greece, Mesogion 152, 115 27 Athens, Greece (dimgrap@yahoo.gr).

Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofw214

Table 1. Demographic, Clinical, and Imaging Features of Our Studied Cases

Patient Number	Gender	Age	Comorbidities	Thromboembolic Event	VTE Risk Factors	Outcome
1	Female	49	Dyslipidemia, hypothyroidism	De novo PE	Infection	-Ward hospitalization -Uncomplicated recovery
2	Male	38	None	De novo PE	Infection Current smoking	-Ward hospitalization -Uncomplicated recovery
3	Male	47	None	DVT + PE	In-hospital immobilization, Infection	-ICU admission. -Uncomplicated recovery
4	Male	73	Coronary artery disease, diabetes mellitus, arterial hypertension	De novo PE	Infection Current smoking	-Ward hospitalization -Uncomplicated recovery
5	Male	54	Arterial hypertension, dyslipidemia	De novo PE	Infection	-Ward hospitalization -Uncomplicated recovery
6	Male	47	None	De novo PE	Infection Current smoking	-Ward hospitalization -Uncomplicated recovery
7	Male	49	Arterial hypertension	De novo PE	Infection Current smoking	-Ward hospitalization -Uncomplicated recovery

Abbreviations: DVT, deep vein thrombosis; ICU, intensive care unit; PE, pulmonary embolism; VTE, venous thromboembolic event.

All patients were ambulatory before hospital admission and had no personal or family history of venous thromboembolic disease. Four patients (cases 2, 4, 6, and 7) were current smokers, and the remaining 3 were never-smokers. Only 1 patient (case 4) had received the seasonal influenza vaccination.

All our cases presented with fever of abrupt onset, either alone or accompanied by cough or dyspnea, and were diagnosed with moderate (cases 1, 2, 4, 5, 6) or severe (case 3) atypical pneumonia. Bacterial infection/coinfection was excluded in all cases by negative sputum cultures for bacterial growth and absence of focal segmental/lobar infiltrates suggestive of bacterial pneumonia on chest films. All patients received antiviral treatment with oseltamivir (75 mg, per os, twice daily for 7 days) starting on the day of their admission to our hospital. Anticoagulation prophylaxis was administered only in 1 patient (case 3), after his admission to the intensive care unit (ICU); all other patients remained ambulatory before the development of VTEs and had no known risk factors for the development of VTEs (other than the presence of acute infection).

Venous thromboembolic events occurred on days 3 to 6 postadmission. Pulmonary embolism without evidence of DVT was diagnosed in 85.7% (6 of 7) of our pH1N1 cases; 1 patient (case 3) developed concomitant DVT and PE, with rapid deterioration of his arterial blood gas levels, requiring intubation and mechanical ventilation in the ICU. None of the other patients required ICU admission. Anticoagulation therapy with low molecular weight heparine was initiated immediately after imaging confirmation of the thromboembolic event. No death or severe complications were recorded. All patients were discharged after becoming afebrile, with instructions to continue receiving anticoagulation therapy at home.

DISCUSSION

In the present series, 6 patients with moderate to severe pH1N1 infection developed PE without evidence of underlying DVT within the first week of their hospitalization for influenza pneumonia. It is interesting to note that the high rate (85.7%) of de novo PE observed in our case series stands in striking contrast to the frequency of PE without DVT (3 of 26 cases, 11.5%) among all noninfluenza patients with PE, admitted during the same time period to our hospital, as well as to the incidence of de novo PE previously reported in the literature (ranging from 0% to 22.6%), with the highest incidence reported in an autopsy study of 500 trauma, surgical, and medical patients with fatal pulmonary emboli [10, 11]. Our clinical observation further supports the results of another autopsy study [8], reporting higher incidence (62.5%) of peripherally distributed pulmonary thrombi among 8 patients with fatal pH1N1 infection, compared with the corresponding rate (37.5%) of peripheral pulmonary thrombi observed in a control group of 8 noninfluenza-related autopsy cases, suggesting the possibility of de novo formation—instead of an embolic migration—of thrombi among pH1N1-infected individuals.

The Centers for Disease Control and Prevention first reported that 5 of 10 ICU patients with pH1N1 infection and acute respiratory distress syndrome developed VTEs [4]. In a subsequent report, vascular incidents were observed in 5 of 20 cases (25%) of severely ill ICU patients with pH1N1 infection [6]. More specifically, DVT was observed in 3 cases, including a pregnant woman aged 40 years old and 2 males with concomitant hematolological malignancy aged 22 and 23 years old, whereas 2 additional patients developed arterial thrombotic events [6]. Gökçe et al [7] reported the case of an adolescent female with PCR-confirmed pH1N1 infection and no significant risk factors for VTEs—other than immobilization—who developed deep femoral vein thrombosis while treated for pH1N1 pneumonia. Similarly to these findings, another study concluded that pH1N1-infected individuals with severe symptoms, in need of ICU admission and mechanical ventilation, may represent a higher risk group for the development of PE, compared with patients with milder pH1N1

disease not admitted to the ICU [9]. It also must be noted that all patients in our series with de novo PE had pneumonia of moderate severity and developed venous thromboembolism during their ward hospitalization; this may suggest that VTEs among patients with pH1N1 infection may not necessarily occur only in cases with severe disease or those admitted to the ICU, but also in patients with moderate symptoms and good general condition.

Bunce et al [5] evaluated the frequency of both arterial and venous vascular complications in pH1N1-infected individuals; among 119 patients included in their series, 4 of 119 (3.4%) developed VTEs, whereas another 3 of 119 patients (2.5%) developed arterial thrombosis. Although the authors failed to document an increased incidence of vascular events in patients with pH1N1 infection, compared with critically ill patients (by other cause), they concluded that the development of massive thromboembolic events and clinically severe arterial thrombosis observed in some of their studied cases may suggest an association between pH1N1 infection and hypercoagulability [5].

Preclinical evidence suggests that influenza viruses may be associated with a state of hypercoagulability, thus potentially predisposing to the development of VTEs. In vitro infection of cultured human endothelial cells from influenza A, among other respiratory viruses, has been shown to stimulate a 4- to 5-fold increase in tissue factor expression, and to induce a prothrombotic endothelial state, via stimulation of the extrinsic coagulation pathway [12]. The procoagulant activity of influenza viruses has also been demonstrated in vivo, in mice with a reduced capacity to generate activated protein C or deficient in plasminogen activator inhibitor type-1 [13]. Furthermore, the inflammatory response itself, via its underlying prothrombotic state, may play a key role in the establishment of arterial and venous thromboembolism [14]. Recent data have further suggested that local inflammation of the lung parenchyma may theoretically contribute to endothelium activation and subsequent induction of a hypercoagulable state in the surrounding microenvironment—similarly to the endothelial response preceding the development of DVT in the extremities—with the potential to progress to local de novo thrombosis of the pulmonary vessels [10, 15, 16].

Well established factors that seem to be strongly and independently associated with an increased risk of VTEs in medical patients primarily include age older than 75 years, active malignancy or acute infection, immobilization, previous VTE, and inherited thrombophilia [17, 18]. Acute inflammatory state was the only major predisposing factor for venous thromboembolism in our cases with de novo PE, thus increasing the probability that pH1N1 infection may have at least contributed to—if not directly caused—the thromboembolic event.

The benefits of influenza vaccination are well recognized and include (moderate) protection not only against infection but also against hospitalization, whereas previous studies have also shown a potential reduction of the risk of severe complications, such as cardiovascular incidents and VTEs in the vaccinated population, especially among nonelderly patients [19, 20]. It is noteworthy that, in accordance with the above findings, the overwhelming majority of patients in our series (6 of 7 cases, 85.7%) had not received the seasonal influenza vaccine. Additional data from future studies will help clarify whether compliance with vaccination recommendations may result in a significant reduction of the incidence of VTEs and other pH1N1-related complications.

Nevertheless, the observations derived from this series should be evaluated in the light of some limitations of our study, mainly including its retrospective design and the small number of cases evaluated. It must also be noted that thorough testing for inherited thrombophilia was not carried out in any of our patients; hence, we were unable to exclude the possibility of a genetic tendency to venous thromboembolism. Furthermore, because all laboratory-confirmed cases of influenza in our hospital during the study period were due to pH1N1, we were unable to include a control group of non-pH1N1 influenza cases and, thus, perform a more analytical evaluation of the potential increased risk of VTEs in general—as well as de novo PE in particular—in the subgroup of cases with pH1N1 infection compared with the corresponding risks in patients with non-pH1N1 influenza.

CONCLUSIONS

In conclusion, we herein described a series of 7 cases with laboratory-confirmed pH1N1 infection who developed VTEs within the first week of their hospitalization for moderate or severe influenza pneumonia. Male predominance and high rate of de novo PE were the most striking characteristics of our patient population. Larger prospective studies are needed to establish whether pH1N1 infection may represent an additional and independent risk factor for the generation of de novo pulmonary arterial thrombi and other vascular events among infected individuals. Clinicians should remain vigilant for the possibility of PE in patients with acute respiratory symptoms and a recent history of confirmed or suspected pH1N1 infection, even in the absence of known risk factors or an underlying DVT, especially during influenza outbreaks.

Acknowledgment

Potential conflicts of interest. All authors: No reported conflicts.
All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. LaRussa P. Pandemic novel 2009 H1N1 influenza: what have we learned? Semin Respir Crit Care Med **2011**; 32:393–99.
2. Broberg E, Melidou A, Prosenc K, et al. WHO European Region and the European Influenza Surveillance Network members of the reporting countries. Euro Surveill **2016**; 21. doi: 10.2807/1560–7917.ES.2016.21.13.30184.
3. Lippi G, Franchini M, Favaloro EJ. Influenza and cardiovascular disease: does swine-origin, 2009 H1N1 flu virus represent a risk factor, an acute trigger, or both? Semin Thromb Hemost **2010**; 36:49–58.
4. Centers for Disease Control and Prevention (CDC). Intensive-care patients with severe novel influenza A (H1N1) virus infection-Michigan, June 2009. MMWR Morb Mortal Wkly Rep **2009**; 58:749–52.

5. Bunce PE, High SM, Nadjafi M, et al. Pandemic H1N1 influenza infection and vascular thrombosis. Clin Infect Dis **2011**; 52:e14–7.
6. Avnon LS, Munteanu D, Smoliakov A, et al. Thromboembolic events in patients with severe pandemic influenza A/H1N1. Eur J Intern Med **2015**; 26:596–8.
7. Gökçe M, Unal S, Aytaç S, et al. Is Swine-origin influenza a predisposing factor for deep vein thrombosis? Turk J Haematol **2012**; 29:174–6.
8. Harms PW, Schmidt LA, Smith LB, et al. Autopsy findings in eight patients with fatal H1N1 influenza. Am J Clin Pathol **2010**; 134:27–35.
9. Agarwal PP, Cinti S, Kazerooni EA. Chest radiographic and CT findings in novel swine-origin influenza A (H1N1) virus (S-OIV) infection. AJR Am J Roentgenol **2009**; 193:1488–93.
10. Schwartz T, Hingorani A, Ascher E, et al. Pulmonary embolism without deep venous thrombosis. Ann Vasc Surg **2012**; 26:973–6.
11. Tadlock MD, Chouliaras K, Kennedy M, et al. The origin of fatal pulmonary emboli: a postmortem analysis of 500 deaths from pulmonary embolism in trauma, surgical, and medical patients. Am J Surg **2015**; 209:959–68.
12. Visseren FL, Bouwman JJ, Bouter KP, et al. Procoagulant activity of endothelial cells after infection with respiratory viruses. Thromb Haemost **2000**; 84:319–24.
13. Keller TT, van der Sluijs KF, de Kruif MD, et al. Effects on coagulation and fibrinolysis induced by influenza in mice with a reduced capacity to generate activated protein C and a deficiency in plasminogen activator inhibitor type 1. Circ Res **2006**; 99:1261–69.
14. Riva N, Donadini MP, Ageno W. Epidemiology and pathophysiology of venous thromboembolism: similarities with atherothrombosis and the role of inflammation. Thromb Haemost **2015**; 113:1176–83.
15. Velmahos GC, Spaniolas K, Tabbara M, et al. Pulmonary embolism and deep venous thrombosis in trauma: are they related? Arch Surg **2009**; 144:928–32.
16. Van Gent JM, Zander AL, Olson EJ, et al. Pulmonary embolism without deep venous thrombosis: de novo or missed deep venous thrombosis? J Trauma Acute Care Surg **2014**; 76:1270–4.
17. Alikhan R, Cohen AT, Combe S, et al. Risk factors for venous thromboembolism in hospitalized patients with acute medical illness: analysis of the MEDENOX Study. Arch Intern Med **2004**; 164:963–8.
18. Lawall H, Oberacker R, Zemmrich C, et al. Prevalence of deep vein thrombosis in acutely admitted ambulatory non-surgical intensive care unit patients. BMC Res Notes **2014**; 7:431.
19. Zhu T, Carcaillon L, Martinez I, et al. Association of influenza vaccination with reduced risk of venous thromboembolism. Thromb Haemost **2009**; 102:1259–64.
20. Cheng AC, Kotsimbos T, Kelly PM; FluCAN Investigators. Influenza vaccine effectiveness against hospitalization with influenza in adults in Australia in 2014. Vaccine **2015**; 33:7352–6.