Pandemic H1N1 Influenza Infection and Vascular Thrombosis

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During the summer and fall of 2009, significant thrombotic events were observed in patients infected with the pandemic H1N1 influenza A virus. In a retrospective chart review of 119 individuals admitted to the hospital with H1N1 virus infection, 7 patients (5.9%) were found to have experienced thrombotic vascular events.

Critically ill and hospitalized patients are at increased risk of developing vascular clots, such as venous thromboembolism (VTE) [1], primarily as a consequence of decreased mobility resulting in venous stasis. Several factors can contribute to this risk, including the presence of an acute inflammatory state. It has also been suggested that infection with seasonal influenza viruses may promote acute arterial thrombotic events, including acute coronary syndromes and stroke [2–3], although evidence is conflicting.

Since the emergence of the pandemic H1N1 influenza virus (pH1N1) in April 2009 [4], much has been learned about the risk factors associated with increased morbidity and mortality in infected individuals. In addition to its apparent predilection for causing severe disease in certain hosts, pH1N1 has been associated with a variety of extra-pulmonary complications, including encephalitis [5] and rhabdomyolysis [6].

In our practice, a number of cases of thrombotic vascular events were observed in patients with pH1N1 infection. These events were striking in terms of the extent of thrombosis in some patients, as well as the fact that a number of patients developed arterial thrombi during the acute phase of illness. The occurrence of both venous and arterial thrombosis raised the possibility that the mechanisms of thrombus formation may have been distinct from those leading to venous thrombosis alone.

A review of other case series and reports of individuals with pH1N1 infection found that only a few had reported the presence of thrombotic or other vascular events [7, 8]. Whether these events were too infrequent to note or were not counted is unclear. Thus, little is known regarding the actual incidence of thrombotic vascular events in patients with pH1N1 infection and whether this infection confers additional risk for thrombosis.

The present study was designed to determine the prevalence of vascular complications among patients admitted to the hospital with pH1N1 influenza and to describe the nature of such vascular events. We first describe a case report of a patient who developed intravascular thrombosis during acute infection with pH1N1.

CASE REPORT

A 50-year-old woman with confirmed pH1N1 influenza and no significant medical history was admitted to the hospital with a 1-day history of fever and respiratory symptoms. Therapy with oseltamivir (75 mg administered orally twice per day), empirical antibiotics, and deep vein thrombosis (DVT) prophylaxis was initiated. Soon afterwards, the patient was transferred to the intensive care unit with progressive respiratory failure that required intubation and mechanical ventilation. Later that day, she was found to have absent lower extremity pulses bilaterally, along with other signs of acute arterial insufficiency (eg, cold lower extremities bilaterally). Abdominal computed tomography with contrast demonstrated a large occlusive thrombus within the infra-renal aorta. She had an urgent embolectomy with bilateral femoral artery stent placement in addition to systemic anticoagulation with intravenous unfractionated heparin. Five days later, she developed recurrent ischemia of her left lower extremity that necessitated a left-sided above-knee amputation. She gradually recovered from her infection and vascular complications and was discharged from our hospital to a rehabilitation hospital 32 days after admission to our facility.

METHODS

A retrospective cohort study was performed after the pH1N1 pandemic (April 2009 through December 2009) at 2 University
of Toronto-affiliated tertiary care academic hospitals in Toronto, Canada, after approval by Institutional Research Ethics Boards. One hospital, the University Health Network, comprises 2 sites with a total of 727 acute care beds and 40 intensive care unit beds. An adjacent hospital, Mount Sinai Hospital, has 460 acute care beds and 16 intensive care unit beds. Only patients admitted to the hospital with a laboratory-confirmed diagnosis of pH1N1 influenza were included in this case series. Patients with pH1N1 influenza were defined as those with positive polymerase chain reaction (PCR) test results on nasopharyngeal swab, endotracheal aspirate, or bronchoalveolar lavage fluid samples (Influenza A and B PCR; Astra Diagnostics). Patients with presumed pH1N1 influenza without laboratory confirmation, as well as those who were not admitted to the hospital, were excluded from our study. A list of patients with confirmed pH1N1 infection was provided by the microbiology laboratory that serves both hospitals.

A chart review of identified cases was performed using a standardized data collection form by 3 trained reviewers (S.H., M.N., and K.S.). Patient demographic information was recorded, and all vascular events were identified from the chart, including clinical notes and diagnostic test reports. Vascular events were defined as thrombotic or embolic events occurring within the venous or arterial circulation. Only vascular events that occurred or were diagnosed during hospitalization were included in the analysis.

Data were analyzed using Microsoft Excel, version 11.0, to provide descriptive statistics related to the incidence of events and association of preselected clinical factors with these events. Statistical analysis was performed using 2-tailed Student's t tests, with a significant difference between groups defined as a P value <.05.

RESULTS

One hundred and nineteen individuals admitted to the hospital with pH1N1 infection were identified (Table 1). Of these patients, 7 had confirmed thrombotic vascular events diagnosed, 4 of which were venous and 3 of which were arterial in origin (Table 2). All patients with thrombotic events had received DVT prophylaxis with subcutaneous unfractionated heparin. Two additional patients with pH1N1 infection had presumed pulmonary emboli, although neither of these cases were confirmed, and they were not included in the analysis. None of the patients with thrombotic events were pregnant.

There was no difference in age or sex between patients with and those without thrombosis. There was a trend towards increased mortality in patients with thrombotic events; specifically, mortality was 31% among patients with thromboses and 8% among patients without thromboses (P = .07). The mean duration of hospitalization was significantly longer for patients with thromboses than it was for patients without thromboses (36 days vs 9 days; P < .001).

DISCUSSION

In this retrospective cohort study, we identified several cases of thrombotic vascular events that occurred in individuals hospitalized with pH1N1 infection. Although the majority of events occurred within the venous circulation, 3 individuals developed arterial thrombi. Notably, several individuals experienced massive thrombotic events. Two patients in our study developed extensive clots with no known underlying thrombophilia. Overall mortality in our cohort was similar to that reported previously for individuals hospitalized with pH1N1 infection.

Possible mechanisms driving thrombosis during infection include increased platelet activation, alterations in the balance of procoagulant and anti-coagulant factors, stasis secondary to immobility, and vascular endothelial dysfunction or activation. The pathogenesis of arterial thrombus formation may be different than that of venous thrombosis and usually arises as a result of endovascular injury or endothelial activation [10]. This process is followed by the elaboration of a variety of proinflammatory mediators with subsequent platelet and coagulation pathway activation [10]. Thus, the presence of significant arterial thrombus formation in several of our patients suggests an additional or alternative mechanism beyond stasis and hypercoagulability that may result in systemic endothelial activation in pH1N1 infection.

When compared with previously published reports of VTE in critically ill patients, our observed rate of vascular thrombosis was comparable to what has been previously described. Various studies, both prospective and retrospective, have found incidence rates of VTE to range from 5%–10% in such patients [1], although rates vary depending on the degree of active surveillance. Patients in our study were not screened routinely for the development of asymptomatic or “clinically silent” vascular events, making it possible that events went unrecognized. Regardless, it is difficult to infer a relation between novel influenza A and the development of vascular thrombi on the basis of incidence rates alone.

There has long been interest in determining whether infections due to seasonal influenza viruses are associated with vascular events and thrombosis. In terms of VTE, studies have yielded conflicting results, with some reporting increased rates of events among those with influenza infection [11] or reduced rates of events among those with vaccination [12]. Other studies, in contrast, have not found a significant association between seasonal influenza infection and VTE [13]. The evidence for an association of arterial thrombosis (eg, myocardial infarction and ischemic stroke) with seasonal influenza...
infection is also conflicting, although a systematic review of the topic found a small but significant benefit in those who received seasonal influenza vaccination, compared with those who did not (relative risk of cardiovascular death, 0.39; 95% confidence interval, 0.20–0.77) [14]. Infection with other influenza strains may carry similar risks of vascular events, which is an association that has been noted for infection with the avian H5N1 influenza strain in animal models [15].

To our knowledge, this study is the first to quantify the rates of vascular complications in individuals hospitalized with pH1N1 infection. Several limitations of our retrospective observational study are worth noting. The relatively low study numbers limited our ability to carry out more-detailed data analysis of potential mechanisms and risk factors. In addition, none of the patients who were identified as having vascular thrombotic events had comprehensive screening for other hypercoagulable states, making it plausible that some events were a result of other predisposing factors.

Future research is needed to assess the relationship between vascular events and pH1N1 infection and the risk factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n = 119)</th>
<th>Patients with no thrombosis (n = 112)</th>
<th>Patients with thrombosis (n = 7)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean years (± SD)</td>
<td>45.2 ± 16.2</td>
<td>45.2 ± 16.1</td>
<td>45.9 ± 20.0</td>
<td>.92</td>
</tr>
<tr>
<td>Range</td>
<td>18–84</td>
<td>18–84</td>
<td>18–80</td>
<td></td>
</tr>
<tr>
<td>Male sex, %</td>
<td>47.9</td>
<td>46.4</td>
<td>71.4</td>
<td>.20</td>
</tr>
<tr>
<td>Mortality, no. (%) of subjects</td>
<td>11 (9.24)</td>
<td>9 (8.0)</td>
<td>2 (30.8)</td>
<td>.07</td>
</tr>
<tr>
<td>Duration of hospitalization, days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean value (± SD)</td>
<td>11.0 ± 18.0</td>
<td>9.5</td>
<td>36</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Range</td>
<td>0–145</td>
<td>0–145</td>
<td>11–100</td>
<td></td>
</tr>
<tr>
<td>Median value</td>
<td>5</td>
<td>5</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Comparisons calculated between patients with and patients without thrombosis. All comparisons were made using 2-tailed Student’s t test. SD, standard deviation.

### Table 2. Details of Patients with Vascular Thrombotic Events

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Sex</th>
<th>Event</th>
<th>Timing of event</th>
<th>Management</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49</td>
<td>M</td>
<td>ST-elevation myocardial infarction</td>
<td>Event 13 days after first symptoms</td>
<td>No therapy</td>
<td>Died in ICU after 12-day hospitalization</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>M</td>
<td>Bilateral massive DVT (femoral and iliac). Presumed pulmonary embolism 11 days later based on acute right heart failure.</td>
<td>Event 5 days after symptoms</td>
<td>Systemic anticoagulation</td>
<td>Died in ICU after 21-day hospitalization; developed spontaneous ICH on day 18 of hospitalization</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>F</td>
<td>Arterial thrombus of infra-renal aorta</td>
<td>Event same day as first symptoms</td>
<td>Surgical embolectomy and bilateral aortoiliac stents; left above-knee amputation</td>
<td>Discharged home after 32-day hospitalization (required ICU care and ECMO)</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>F</td>
<td>Deep venous thrombosis in left arm</td>
<td>Event 25 days after first symptoms</td>
<td>Systemic anticoagulation</td>
<td>Discharged after 28 days (required ICU care and ventilation)</td>
</tr>
<tr>
<td>5</td>
<td>46</td>
<td>M</td>
<td>Thrombosis of right external iliac vein and common femoral vein</td>
<td>Event 33 days after first symptoms</td>
<td>No therapy</td>
<td>Discharged after 100 days (required ICU care and ventilation)</td>
</tr>
<tr>
<td>6</td>
<td>84</td>
<td>M</td>
<td>Pulmonary embolism</td>
<td>Event 3 days after first symptoms</td>
<td>Systemic anticoagulation</td>
<td>Discharged after 46 days (required ICU care and ventilation)</td>
</tr>
<tr>
<td>7</td>
<td>39</td>
<td>M</td>
<td>ST-elevation myocardial infarction</td>
<td>Event 10 days after first symptoms</td>
<td>Percutaneous coronary angioplasty</td>
<td>Developed left ventricle thrombus; discharged after 11-day hospitalization</td>
</tr>
</tbody>
</table>

**NOTE.** DVT, deep vein thrombosis; ECMO, Extracorporeal membrane oxygenation; ICU, intensive care unit.
associated with thrombotic events. Such studies may be difficult, because it is unclear whether this particular viral strain will re-emerge as a dominant strain of influenza virus in the future. Additional work could also address the possible mechanisms for these effects, focusing on both vascular endothelial changes and alterations in coagulation.

In conclusion, infection with the pH1N1 did not appear to be associated with higher rates of vascular complications than has previously been reported among critically ill patients. However, the development of massive venous thrombotic events and clinically significant arterial thrombosis, as observed in our study cohort, suggests the possibility of pH1N1-associated hypercoagulability and endothelial activation and/or dysfunction in affected individuals.

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**References**