



Original Article

Thromboembolic events in patients with severe pandemic influenza A/H1N1

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ABSTRACT

Background: 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 A/H1N1 pneumonia resulted in an increased need for ICU beds. Several risk groups were identified that were at a higher risk for adverse outcomes. Pregnant women were a particularly vulnerable group of patients. The CDC reported on the first ten patients with severe illness and acute hypoxemic respiratory failure associated with A/H1N1 infection, none of whom were pregnant, but they noticed that half of the patients had a pulmonary embolism.

Methods: During a four-month period from September to December 2009, 252 patients were admitted to our hospital with confirmed pandemic influenza H1N1 by real-time reverse transcriptase-polymerase chain reaction test (rRT-PCR). We cared for twenty patients (7.9%) admitted to MICU with severe A/H1N1. Results on Thrombotic events were identified in five (25%) of our critically ill patients.

Conclusions: We recommend that patients with severe influenza A/H1N1 pneumonitis and respiratory failure be administered DVT prophylaxis in particular if there are additional risk factors for TVE. Further prospective studies on the relationship of influenza A/H1N1 and VTE are needed.

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1. Introduction

The 2009 pandemic influenza A/H1N1 developed as a novel swine influenza which caused more diseases among younger age groups than in the elderly [1]. Although not as devastating as the 1918 Spanish Flu, it did cause more than 17,700 deaths worldwide. Severe hypoxemic respiratory failure from A/H1N1 pneumonia resulted in an increased need for ICU beds [2]. Several risk groups were identified that were at a higher risk for adverse outcomes [2]. Pregnant women were a particularly vulnerable group of patients; in the Californian cohort of 94 pregnant women with A/H1N1, 18 required ICU admissions and among them 6 died [3]. The CDC reported on the first ten patients with severe illness and acute hypoxemic respiratory failure associated with A/H1N1 infection, none of whom were pregnant, but they noticed that half of the patients had a pulmonary embolism [4]. This is in contrast to the findings from a Dutch group that patients with proven pulmonary embolism were less likely to have evidence of recent influenza illness than a control group in whom pulmonary embolism had been ruled out [5].

We report our experience with five patients that suffered clinically striking thrombotic events among 20 patients admitted to the medical intensive care unit (MICU) with severe A/H1N1.

2. Methods and results

During a four-month period from September to December 2009, 252 patients were admitted to our hospital with confirmed pandemic influenza H1N1 by real-time reverse transcriptase-polymerase chain reaction test (rRT-PCR). We cared for twenty patients (7.9%) admitted to MICU with severe A/H1N1 (Table 1); seven men and 13 women. Their mean age (SD) was 36 (14) years (range: 19–67). None had received vaccination. All patients received oseltamivir as soon as the suspicion of A/H1N1 was raised in addition to broad spectrum AB. Fourteen patients (67%) developed ARDS with intractable hypoxemia and needed prolonged mechanical ventilation with nitric oxide and prone position. Five of our 13 women were pregnant (38.5%); they underwent three 2nd semester pregnancy losses; two 3rd trimester emergency cesarean sections (CS) with the delivery of healthy babies that survived.

Thrombotic events were identified in five patients (25%) of our critically ill patients (Table 2). Two of these patients did not receive DVT prophylaxis as they had thrombocytopenia after chemotherapy for their hematological malignancy; one of whom also received an inferior vena

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Table 1
Our patients.

	Patients without VTE	Patients suffering VTE
Number	15/20	5/20 (25%)
Male/female	6/9	2/3
Mean aged (SD) years	39.5 (15.7)	26.4 (8.3)
Bedouins	9	4
Mortality in MICU	1	2
Mortality 30 days	3	2
60 days	4	2
<i>Comorbidities</i>		
Pregnancy	2	3
Malignancy	2	2
	Lung cancer	s/p induction for B cell lymphoma
	s/p AML 7 years	s/p initial cycle for AML
Obesity	2	0
s/p transplantation	2	0
	s/p heart transplant 8 weeks	
	s/p bone marrow AML 7 years	
Asthma	2	0
Liver cirrhosis	1	0
DM	1	0
Kidney disease	1	0
None	1	0

cava filter for that same reason. There were two surprising arterial thrombotic events in two young pregnant women: extensive ischemic cerebrovascular event (CVA) and an acute myocardial infarction. The patient with CVA had an elevated anti-cardiolipin (IgG: 25/5 U/ml) when the CVA was diagnosed but it returned to normal four months later. Among these five patients two of the pregnant women died (Table 2). The patient with

acute myocardial infarction and the woman after emergency cesarean section suffered a subclavian and external jugular vein DVT without a prior central line. The patient with CVA underwent rehabilitation and her aphasia improved but she has hemiparesis and needs a wheel chair when she leaves her home.

3. Discussion

We reported on five patients (25%) among 20 severely ill ICU patients with proven A/H1N1 pandemic infection, who experienced a clinically significant thrombotic event among them two arterial thrombotic events in two young pregnant women: CVA and acute myocardial infarction. Three patients had DVT without an underlying central line. All three women were pregnant and two of them succumbed to their severe illness.

One report has described thromboembolic events (TVE) as a complication in proven A/H1N1 infection [6]. Among 112 patients with severe as well as mild H1N1 disease they identified seven patients with VTE (6.3%), including acute myocardial infarction in two, deep vein thrombosis (DVT) in three and one patient with an arterial thrombosis. The presence of vascular thrombosis was associated with increased mortality (30% versus 8%) [6]. Interestingly, none of their seven patients were pregnant [6]. In the first report from the CDC on ten patients with severe ARDS from A/H1N1 it was noted that 5 had pulmonary embolism (50%) and it was recommended to use DVT prophylaxis [4]. None of these ten patients were reported to have been pregnant [4]. Our three pregnant patients did receive DVT prophylaxis with subcutaneous unfractionated heparin.

The first autopsy report on 21 patients with confirmed A/H1N1 infection identified four (19%) with pulmonary embolism [7]; another USA autopsy study on eight patients, revealed pulmonary embolism in

Table 2
Thrombotic complications in our patients with influenza A/H1N1.

Gender age/ethnic	Admitted from/LOS MICU/all LOS days; outcome:	Co-morbidity	ICU management In addition to oseltamivir	ICU complications	Thrombotic complications
Patient 1. F 19/Bedouin	From ED 66/227 Survived	Pregnancy 21 weeks, spontaneous abortion day 1	MV day 1, Muscle relaxants; Vasopressors; Prone position Nitric oxide Sc heparin 5000 U x3 Iv Rocefin Iv perimivir X2	Intractable hypoxemia, Concomitant pneumococcal bacteremia, Polyneuropathy Bilateral barotraumas Prolonged fever Prolonged H1N1 secretion (4 weeks) Intractable hypoxemia	CVA bilateral diagnosed day 34 Aphasia and left hemiparesis ECHO: sinus tachycardia. Normal left and right ventricular size and function. NO valvulopathy Acute anterior ST elevation MI day 2 ECHO: sinus tachycardia. Severe left ventricular dysfunction. Global hypokinesis. Preserved right ventricular function.
Patient 2. F 28/Bedouin	From ED 13/13 Deceased	Pregnancy 24 weeks;	MV day 2; Muscle relaxants Vasopressors Prone position Sc heparin 5000 U x3	Intractable hypoxemia Leukopenia on admission 2600 Barotraumas	DVT of subclavian and jugularis vein in bedside duplex day 16 (no central line on that side)
Patient 3 F 40/Bedouin	From OR after CS 36/37 Deceased	Pregnant 36 weeks; emergency CS before admission to MICU	MV in OR (37 days) Vasopressors Nitric oxide Prone position Sc heparin 5000 U x3 Iv rocefin, azenil	Intractable hypoxemia Leukopenia on admission 2600 Barotraumas	DVT of subclavian and jugularis vein in bedside duplex day 16 (no central line on that side)
Patient 4 M 23/Jewish	From ED 36/66 Survived	Cerebral palsy; after induction chemo-therapy for B cell Lymphoma (CHOP).	MV on day 4 (for 36 days) Tracheostomy Muscle relaxants; Iv tazocin	Neutropenic fever after chemotherapy; Concomitant <i>Staph aureus</i> furunculosis of skin MV day 3 Bilateral barotraumas Guillain Barre	DVT left subclavian day 15 (no central line on that side) did not receive sc heparin for DVT prophylaxis d/t post-chemotherapy thrombocytopenia;
Patient 5 M 22/Bedouin he was admitted twice on both admissions A/H1N1 was positive 18 days apart	11/41 Survived	On second admission with neutropenic fever after induction therapy for new diagnosed AML	MV on admission (14 days) Vasopressors Iv rocefin ciproxin		DVT of rt leg day 5 (no central line); due to chemotherapy induced thrombocytopenic did not receive prophylactic sc heparin. Had inferior vena cava filter inserted

LOS: length of stay.

two, and DVT and portal vein thrombosis in one each, i.e. half their patients had suffered VTE [8]. This in contrast to a Spanish report on 382 patients with ARDS not related to A/H1N1 viral pneumonitis, they found three patients with pulmonary embolism among the patients in whom diffuse alveolar damage was not revealed at the post-mortem examination although clinically and physiologically they were diagnosed as ARDS [9]. This highlights the fact that patients with severe A/H1N1 infection suffered a high frequency of VTEs more so than patients with usual causes of ARDS and sepsis, and that arterial thrombosis is of particular concern as seen in two of our patients with CVA and acute myocardial infarction. Among our fourteen patients with severe ARDS and hypoxemic respiratory failure it could be questioned whether undetected pulmonary embolism contributed to the intractable hypoxemia they experienced; we did not systematically investigate our patients for this but they were administered DVT prophylaxis with unfractionated heparin.

Pregnancy and the post-partum period are known to be hypercoagulability states and in the developed world pulmonary embolism is an important cause of maternal mortality [10]. But in a review of pregnant Californian women with A/H1N1 infection VTE was not reported as a complication [3]. Furthermore in the Australian cohort of pregnancy associated critical ill patients with A/H1N1, VTE was not reported as a complication [11].

In the Brazilian autopsy study three distinct pathological patterns were described in the lungs of patients succumbing to A/H1N1 infection: extensive diffuse alveolar damage (DAD) present in nine of their patients; this is the pattern associated with ARDS. Six patients had necrotizing bronchiolitis and five patients had DAD with intense alveolar hemorrhage [7]. In our practice hemoptysis was not a clinical complication among our patients on mechanical ventilation for A/H1N1 pneumonitis.

Two of our pregnant patients suffered an arterial thrombosis, extensive CVA and an acute myocardial infarction. Acute myocardial infarction is rare among pregnant women; a recent review for the period 2006–2011 identified 150 reported patients with pregnancy-associated-acute-myocardial-infarction (PAMI) with a fatal outcome in nine patients (7%) [12]. Only 37 women with PAMI (24.7%) were younger than 30 years of age, like our patient. PAMI is more frequent in the third trimester and post-partum and only 25 (16.7%) occurred during the second trimester. PAMI was associated with coronary dissection (43%), atherosclerosis (27%), clot formation (17%), spasm (2%) and Takotsubo cardiomyopathy (2%); while 11 (9%) had normal coronary arteries [12]. In our patient it was impossible to perform coronary angiography due to her severe ARDS thus it could be argued that she may have had Takotsubo cardiomyopathy. Interestingly acute infections were not mentioned as a cause of PAMI [12].

Arterial thrombosis has been associated with increased levels of von Willebrand factor which is also increased during advanced pregnancy [13]. It may be speculated that bleeding in the lungs as identified in autopsy studies may have contributed to the activation of the von Willebrand factor thus predisposing for developing arterial thrombosis.

Our two male patients with DVT were in their initial treatment cycles for hematological malignancy. Patients with lymphoma are at a higher risk for developing VTE during the initial cycles of treatment than during later cycles [14].

It is common practice to administer DVT prophylaxis to ICU patients with severe illness although the risk of administering DVT prophylaxis should be weighed against the risk of bleeding [15].

A peculiar propensity for thrombotic events has been reported for cytomegalovirus (CMV) infection; nine Israeli immune-competent patients with CMV associated thrombotic events, two of whom were arterial thrombosis (spleen and liver) [16]. The pathogenic mechanisms are unknown but among a number of mechanisms suggested that an increased level of von Willebrand factor was seen with higher levels of CMV titers in plasma [15]. It was noted that simultaneously with CMV infection IgM anticardiolipin antibodies appeared leading to acquired anti-phospholipid syndrome [16]. Our patient with CVA did

have increased levels of IgG anticardiolipin that disappeared four months later.

Since the 2009/2010 pandemic there have been sporadic patients with H1N1 illness as well as other viral illnesses, but during the last few years patients with influenza like illness admitted have not presented with very severe hypoxemic respiratory failure that we saw during the pandemic. Public health predictions foresee that it is only a matter of time before the next pandemic arrives.

In conclusion: we report on five patients (25%) with severe influenza H1N1 that developed clinically significant VTE events among 20 patients admitted to MICU during four months of the influenza A/H1N1 pandemic 2009, this included three of the five pregnant women (60%). Forty percent of the VTE were surprising arterial thrombosis with an extensive CVA and an acute myocardial infarction, the latter pregnant woman is deceased. All patients had additional hypercoagulability states: pregnancy and under initial chemotherapy for hematological malignancies that definitely rendered our patients prone for thrombotic events. The arterial thrombotic events were surprising and unusual in such young patients. We recommend that patients with severe influenza A/H1N1 pneumonitis and respiratory failure be administered DVT prophylaxis in particular if there are additional risk factors for TVE. Further prospective studies on the relationship of influenza A/H1N1 and VTE are needed.

Conflict of interests

The authors have no conflicts of interest to report and they have not been paid for the work submitted.

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