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Full Length Research Paper

Preliminary experience of the clinical and tomographic characteristics of patients with non-refractory acute respiratory insufficiency caused by H1N1 influenza, a virus infection and disease intervention

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The HIN1 influenza A virus infection has spread rapidly worldwide, and although it is believed to have a low mortality rate, once the virus reaches the acute refractory respiratory insufficiency phase, the mortality rate increases drastically. This study reports the results of 10 clinical case studies; the patients presented signs and symptoms of acute respiratory insufficiency and were positive for the H1N1 influenza A virus. The characteristics of the patients were the following: mean age was 28.5 ± 15.4 SD., the mean time of patient hospitalization was 12.5 days ± 10.9 SD., the mean values of interleukin 6 were: 17.8 ± 9.9 SD., the mean level of SaO_2% was 91.3 ± 2.5 SD., the mean values for respiratory frequency were 28.8 ± 4.2 SD., and the mean values of arterial PO2 were 59.99 ± 9. The most frequent findings on high resolution computerized tomography findings were the thickening of the peribronchovascular space (90%), followed by intralobular septa thickening (50%), subpleural septa thickening (30%), bronchioectasis (40%), mosaic image of perfusion (40%), and pulmonary condensation zones (30%). Two patients required non-invasive mechanical ventilation that was set to a low exhaled tidal volume of 200 ml for the patient weighing 42 kg and 300 ml for the patient weighing 60 kg. The findings on the HRCT in these patients represent a precocious interstitial lung lesion. The authors believe that an early intervention could prevent the disease progression and the onset of the refractory phase that subsequently leads to hypoxemia and diffuse alveolar damage.

Key words: H1N1 influenza A virus infection, non-invasive mechanical ventilation, high-resolution computerized tomography

INTRODUCTION

Since April 2009, the World Health Organization (WHO) has reported cases of patients infected with the new H1N1 influenza A virus in Mexico and the United States. This has spread worldwide rapidly (Pérez-Padilla R, et al. (2009)). In Ecuador, the first reported case of H1N1 influenza A virus occurred on May 15, 2009, the patient was a child from Guayaquil who had recently traveled to Miami.

On June 11th, 2009, the World Health Organization classified the spread of the disease as an imminent pandemic (stage VI according to the WHO classification). This level of alert does not specify the clinical severity of the disease; instead it classifies the geographical extension. Even though the rate of mortality of the disease has lowered so far, the evolution of the virus is unpredictable (CDC., 2009).

The course of the disease has a wide spectrum of clinical findings, ranging from patients who are presented with no fever and mild infections of the lower respiratory tract to fatal pneumonias leading to respiratory distress. This article presents the description of 10 case studies of acute respiratory insufficiency and infection due to H1N1

influenza A virus, emphasizing the clinical manifestations, arterial blood gas analysis, and high-resolution computerized tomography (HRCT) findings.

The treatment protocol applied for early medical intervention is also proposed in this article, which consists of oseltamivir, antibiotics, bronchodilators, low-dose corticosteroids, and noninvasive mechanical ventilation (NIMV).

MATERIALS AND METHODS

This research study was performed at Guayaquil's military hospital, in the city of Guayaquil, Ecuador. The military hospital is a medical center specializing in the treatment and the management of patients suffering from diseases related to the respiratory system. The area is designated for hospitalization – it consists of 108 beds and specialized equipment for the treatment, evaluation, and management of patients with respiratory pathology.

Selection criteria

All patients who arrived at the ER at the Military Hospital from July 22, 2009 through September 11, 2009 who had symptoms suggestive of H1N1 Influenza A virus were included in the study. Consent was obtained from the patients or their relatives if they were unable to do so. This study was approved by the Ethics Committees of University of San Francisco de Quito and by the military hospital in Guayaquil-, Ecuador.

Clinical symptoms included: fever >38.5°C, arthralgias, myalgias, headache, nasal obstruction, productive cough, and acute respiratory insufficiency (respiratory rate > 25 breathes per min and hypoxemia measured by a partial pressure of arterial oxygen (PaO_2) of < 60 mmHg.)

Non-refractory acute respiratory insufficiency and H1N1 Influenza A

All the patients who at the time of the emergency room evaluation had a respiratory rate greater than 25 breathes per min, with or without bronchospasm, and an O_2 saturation < 93% without complementary oxygen were placed in the nonrefractory acute respiratory insufficiency group

Interventions and measurements

After performing a nasopharyngeal swab on all patients who had the signs and symptoms suggestive of H1N1 influenza A, the samples were gathered and then evaluated for quantitative C-reactive protein levels (CRP). CRP is a marker for bacterial infection and inflammation. CRP was measured by immunoturbidimetry in an automatic autoanalyzer HITACHI 747 using a commercial kit (Roche Diagnostics Systems). The upper normal limits were 5 mg/L^{-1} for CRP. The sample was also evaluated for a complete blood count, LDH levels, and serum interleukin 6 levels. Radiologic studies were performed on each patient, and they included a standardized PA and lateral chest X-ray followed by HRCT. Additionally, blood samples for culture studies, urine culture, and a sputum culture were collected for further analysis.

Sampling for H1N1 Influenza A

Specimens from nasopharyngeal swab were collected and stored at a temperature between 2 and 4°C to ensure their adequate transportation to the Institute Nacional de Higiene de Guayaquil", where the microbiology department of the Public Health Ministry MSP performed the sample processing are located. RT-PCR for H1N1 influenza A tests were done according to standardized guidelines provided by the U.S. Center for Disease Control and Prevention.

Radiologic and tomographic studies

Standardized PA and lateral chest X-rays were obtained from every patient. 10 mm sections from computed axial tomography with contrast injection were executed and then followed by a 1.5 – 2 mm section in high-resolution computerized tomography findings (HRCT). All scans were carried out at full inspiration. Radiological studies were performed by two experienced radiologists.

Early intervention protocol

Oxygen therapy

All patients received supplemental oxygen by means of nasal cannula, avoiding high oxygen concentration to maintain the partial pressure of arterial oxygen (PaO_2) between 100 and 105 mmHg Bronchodilator therapy 200 mcg Albuterol/36 mcg + Ipatropium Bromide was used every 2-4 h with a metered-dose inhaler with a space (AeroChamber).

Corticosteroid therapy

It was initiated early in the treatment course in patients who presented bronchospasm and high systemic inflammatory response reflected by high levels of interleukin 6. Low-dose hydrocortisone (100 mg every 8-12 h) was combined with inhaled corticosteroids (Budesonide 400 mcg + Formoterol) in patients who presented acute respiratory insufficiency, (with respiratory rate between 25- and 40).

Antibioticotherapy

All the patients with levels of quantitative PCR > 5 mg/L^{-1} received ampicilline/sulbactan of a dose of 3 g IV every 8 h for bacterial infection.

Antiviral therapy

Oseltamivir was used in all the patients in doses of 75 mg, every 12 h since the initial diagnostic confirmation for the disease.

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Abbreviations: HRCT, High-resolution computerized tomography; **IL-6,** interleukin 6; **WHO,** world health organization; **IPAP,** inspiratory positive airway pressure; **EPAP,** expirztory positive airway pressure; **NIMV,** noninvasive mechanical ventilation; **HR,** heart rate; **RR,** respiratory rate; **ER,** emergency room (ER).

NIMV protocol

For the NIMV a *KnightStar® 335* (manufactured by Puritan-Bennett Corporation Tyco Healthcare, UK) was used. The control settings were placed at A/C modality with BACKUP f (respiration rate of 15) and ISENS 3, ESENS 3, RISE TIME 20. IPAP and EPAP levels were initially set to 11 and 6 cm^2 H_2O, respectively. Ultra Mirage series III (manufactured by Resmed) was also used.

NIMV therapy was initiated on a non-interruption 6-h mode that was carefully monitored by a respiratory technician, an NIMV trained medical resident, or by the attending physician. The initial 6-hour setting was later changed to a 3-h interval setting, in which the tolerance and the patient response were monitored by a respiratory technician or the head nurse. Weaning was initiated after correct stabilization of clinical parameters. This protocol was pursued as long as the patient's tolerability allowed it. All data were expressed as mean +/- SD for all numeric variables and percentages for all the nominal variables.

RESULTS

The mean age of the patient was 28.5 +/- 15.4 SD, the mean hospitalization time was 12.5 days +/- 10.9 SD, and the mean number of days from the beginning of symptoms until admission was 2.4 +/- 0.7 SD. The mean temperature was 38.9°C +/- 0.6 SD. Descriptive variables are as shown in Table 1. The most frequent symptoms were fever, cough, and sputum production as shown in Table 2.

All the radiologic findings are shown in Table 3 and are the computerized tomographic image results. The most frequent findings on HRCT were thickening of the peribronchovascular space (90%), followed by intralobular septa thickening (50%), subpleural septa thickening (30%), bronchioectasis (40%), mosaic image of perfusion (40%), and pulmonary condensation zones (30%) (Tables 3, 4 and Figures 1, 2, 3 and 4). From the 10 case studies, only 2 of the patients required NIMV, which is shown in Table 5.

DISCUSSION

The purpose of the study was to describe the clinical manifestations, as well as the laboratory and radiologic findings of 10 patients who tested positive to H1N1 influenza A with non-refractory acute respiratory insufficiency.

From the results, a marked predominance of the disease for young patients (mean of 28.5 years ± 15.4 SD) is observed. The most common symptoms that the patients experienced were fever and a productive cough accompanied by arthralgias and myalgias. These findings were consistent with the Mexican group's study guided by Pérez-Padilla et al. (2009).

For the 10 patients, the mean body mass index was 25, with a range of 13.7 – 33.3. It has been observed and reported in other studies that a high body mass index is correlated with a poor disease prognosis and outcomes (Akinnusi et al., 2008).

The most common findings in HRCT were thickening of the peribronchovascular space that was seen most frequently, and thickening of the intralobular and subpleural septa.

The 10 patients presented levels of IL-6 in peripheral blood samples (mean: 17.8; range: 2 – 33.8), showing that the damage and the clinical course of the illness depend on the immunologic reaction mediated by inflammatory cytokines in response to viral replication.

Even though all cultures were negative, the possibility of concomitant bacterial infection should be taken into consideration. It has been observed that PCR can be used as an acute infection biological marker of disease severe in patients with respiratory tract infections (Menéndez, 2008; Collazos, 2007; Simon, 2004). Only 2 out of the 10 patients had a concomitant neuromuscular disorder; this baseline disease affected the course of the H1N1 influenza A virus infection, making the respiratory insufficiency more profound and severe. Those patients who received NIMV had associated neuromuscular alterations during the treatment course.

The majority of complications in patients with H1N1 influenza A have been reported in those with concomitant medical conditions, however, the highest mortality rates are seen in young patients without other medical conditions (Hanshaoworakul et al., 2009)

The sequential treatment for non-refractory acute respiratory insufficiency with oxygen, bronchodilators, low doses of corticosteroids, and NIMV, is believed to have prevented the use of invasive mechanical ventilation.

This study establishes that the use of NIMV in the early stages of the disease might be of great value. Of the 10 patients, the 2 who had neuromuscular comorbidity were given NIMV. Although NIMV is not recommended for patients with refractory hypoxemia and shock, earlier intervention is believed to alter the disease prognosis ultimately producing a more favorable outcome. For those patients with refractory hypoxemia, the NIMV was set to a low exhaled tidal volume of 200 ml for the patient weighing 42 kg and 300 ml for the patient weighing 60 kg.

The mechanical properties of the 2 patients who received NIMV suggest that addressing the neuromuscular problem first could be a determinant for the successful recovery of these patients. One 21-year-old male patient, without any comorbidities had a successful recovery with the use of bilevel mode mechanical respiration (BiPAP: bilevel positive airway pressure) (Intensive-care patients with severe novel influenza A (H1N1) virus infection, 2009) From the authors' experience and observations in this study, the use of non-invasive mechanical ventilation is the determinant factor for success in the treatment of refractory respiratory insufficiency caused by the H1N1 influenza A virus (Briones, 2008; Carlucci, 2003).

Oseltamivir was used in all the patients in doses of 75 mg, every 12 h, immediately after diagnosis confirmation. Observational studies now show a significant reduction in mortality

Table 1. Descriptive characteristics of the 10 patients with H1N1.

	Minimum	Mean	Maximum	Standard deviation
Age	15.0	28.5	53.0	15.4
Days of hospitalization	7.0	9.4	13.0	2.1
Start of symptoms - hospitalization	1.0	2.4	3.0	0.7
Average of sample reports	0.0	1.3	2.0	0.7
BMI	13.7	25.0	33.3	6.8
Fever	38.0	38.9	40.0	0.6
Leukocytes	4600.0	7600.0	10200.0	1537.7
Segmented	41.4	64.1	80.3	14.9
Linphocytes %/L	12.1	26.5	48.6	13.5
Monocytes %/L	6.6	9.3	15.3	3.7
Eosinophils %/L	0.2	2.1	8.4	2.8
Basophils	0.2	0.3	0.6	0.1
HCT	31.8	40.9	43.4	3.4
MCV	82.0	93.1	98.8	5.1
MCH	27.0	29.5	32.0	1.5
MCC	29.2	31.8	35.0	1.9
Platelets	152.0	238.1	327.0	47.0
LDH	338.0	642.2	1110.0	200.3
Na	133.4	139.0	143.0	2.7
K	2.9	4.1	4.6	0.5
Cl	97.7	102.9	108.0	2.6
Creatinin	0.7	0.9	1.4	0.2
Glucose	88.0	101.6	120.0	10.5
Quantitative PCR (bacterial infection)	8.3	35.7	121.5	39.4
Interleukin 6	2.0	17.8	33.8	9.9
SaO_2% by pulse oximetry	85.0	91.3	93.0	2.5
HR (Beats/min)	90.0	102.2	128.0	11.8
RR (Resp/min)	26.0	28.8	40.0	4.2
Systolic pressure	90.0	110.0	130.0	13.3
Diastolic pressure	60.0	64.0	80.0	7.0
pH	7.29	7.35	7.44	0.06
PCO_2	27.20	40.75	51.40	7.99
EBP	-9.50	-2.42	8.20	5.57
PO_2	43.20	59.99	68.50	9.36
H_3CO	14.9	22.06	32.1	5.286

*Data expressed in mean+- Standard deviation and minimum and maximum. HCT= Hematocrit; MCV= Mean corpuscular volume; MCH= Mean corpuscular hemoglobin; BMI= Body mass index; LDH= Lactate dehydrogenase in peripheral blood; MCC= Concentration mean corpuscular; LDH; Lactato Deshidrogenasa en sangre periferica; Na= Sodium concentration in plasma; K= Potassium concentration in plasma; Cl= Chlorine concentration in plasma; SaO_2% by Pulse Oximetry= Peripheral oxygen saturation measured in finger; HR= Number of heart beats in 1 min; RR= Number of respirations in 1 min; pH= Hydrogen ions concentration; PCO_2= Partial pressure of Carbon Dioxide; EBP= Excess of base; H_3CO= Bicarbonate concentration in blood.

rates for patients hospitalized with seasonal influenza compared with those who were not hospitalized (McGeer, 2007; Harper, 2009). Although early treatment (<48 h) is ideal (Abdel-Ghafar et al., 2008), the mortality rate was also reduced when treatment was started >48 h after diagnosis (Treanor et al., 2000).

Although the use of corticosteroids is not recommended in patients with H1N1 influenza A, a low-dose of hydrocortisone (100 mg every 12 h) was combined with inhaled corticosteroids (Budesonide 400 mcg + Formoterol) in patients who presented acute respiratory insufficiency, measured by the respiratory rate of 28.2 (24-40), and bronchospasm. Confalonieri et al. (1999) and Annane et al. (2004) recommend the use of corticosteroids in patients who present specific conditions associated with pneumonia and to prevent the evolution to septic shock. The use of low dose corticosteroids in 5 of 10 patients with acute respiratory failure and novel

Table 2. Frequent symptoms of the 10 patients.

Clinical symptoms	Present (%)	Absent (%)
Fever	10 (100)	0
Cough	10 (100)	0
Sputum production	10 (100)	0
Sore throat	9 (90)	1 (10)
Nasal obstruction	9 (90)	1 (10)
Headache	9 (90)	1 (10)
Myalgias	9 (90)	1 (10)
Arthralgias	9 (90)	1 (10)
Hemoptysis	1 (10)	9 (90)
Nausea	1 (10)	9 (90)
Vomit	1 (10)	9 (90)
Diarrhea	1(10)	9 (90)

*Data expressed in percentages.

Table 3. Radiologic findings from 10 H1N1 patients with acute respiratory insufficiency.

Patients	Unilateral	Bilateral	Normal	Infiltrate	Reinforcement in bronchovascular pattern	Flattened diaphragm
1	-	-	+	-	-	-
2	+	-	-	+	-	-
3	+	-	-	+	-	-
4	-	+	-	+	-	-
5	-	+	-	+	+	-
6	-	-	+	-	-	-
7	+	-	-	-	+	-
8	+	-	-	+	+	-
9	+	-	+	-	-	-
10	-	+	-	+	-	+

*Data expressed + (present) - (absent).

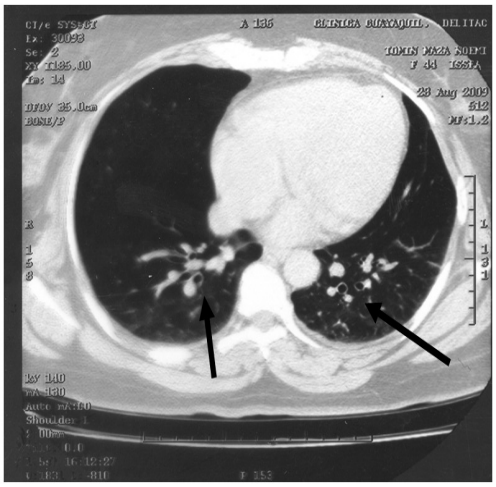
Table 4. Findings in HRCT of 10 patients with H1N1 influenza A and acute respiratory insufficiency.

Patients	Thickening of peribronchovascular space	Thickening of intralobular septa	Thickening of subpleural septa	Bronchoectasis	Ground-glass sign imaging
1	+	-	-	+	-
2	+	+	-	-	-
3	+	+	+	+	-
4	+	+	-	+	-
5	+	+	-	-	+
6	+	-	+	-	-
7	+	-	-	-	-
8	+	-	-	-	-
9	-	-	-	-	-
10	+	+	+	+	-

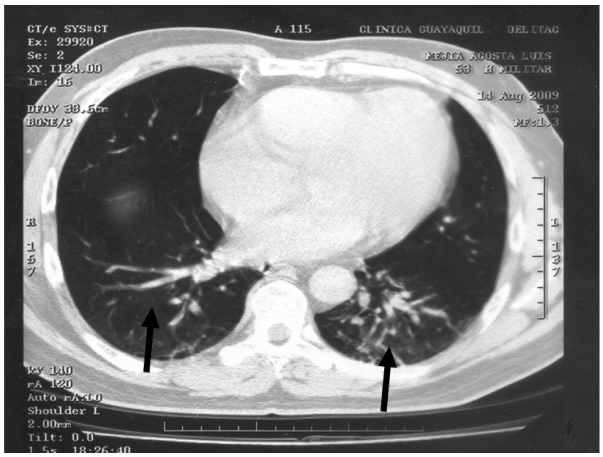
Table 4. Cont'd.

Mosaic perfusion	Adenopathies	Condensation zones	Fibrotic Bands	Atelectasic bands	Posterior basal thickening
-	-	-	-	-	-
+	-	+	+	-	-
-	-	-	-	+	-
-	+	-	-	-	-
+	-	+	-	+	-
-	-	-	-	+	+
-	-	-	-	-	-
-	-	+	+	+	-
+	-	-	-	-	-
+	-	-	+	-	-

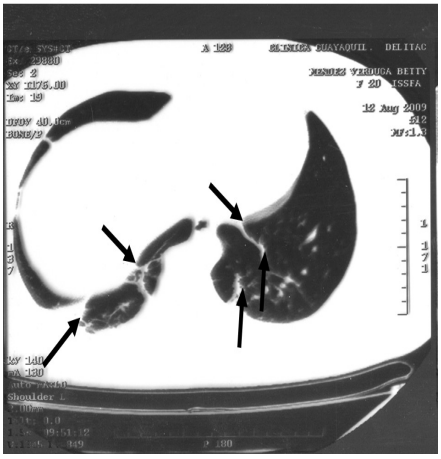
*Data expressed (+) present sign ; (-) absent sign HR-CCT: High-Resolution Contrasted Computerized Tomography



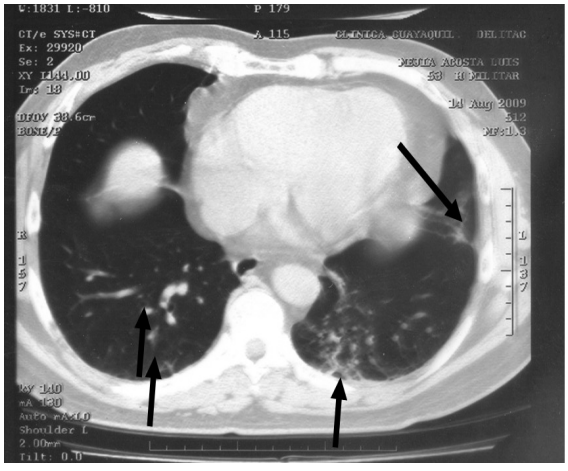
Picture 1. Bilateral cylindrical bronchioectasis in lateral basal segments.



Picture 3. Thickening of peribronchovascular space and subpleural septa.



Picture 2. Thickening of subpleural septa and atelectasic bands.



Picture 4. Thickening of intralobular and subpleural septa with condensation zones in lingular left inferior segment.

Table 5. Patients with noinvasive mechanical ventilation.

Patients	Days with noinvasive mechanical ventilation	IPAP	EPAP	Control model	BACKUP f Backup respiration rate (in A/C mode)	ISENS	ESENS	Rise time	Vt	i/E Relation	Leak	Patient (RR)
Patient 3	1 day	12	6	A/C	15	3	3	20	200	1,2,3	20	40
	2 day	11	5	A/C	15	3	3	20	550	1,2,9	25	28
	3 day	11	5	A/C	15	3	3	20	600	1,3,0	10	25
	4 day	11	5	A/C	15	3	3	20	700	1,3,5	5	20
Patient 4	1 day	12	6	A/C	15	3	3	20	300	1,2,1	8	30
	2 day	12	6	A/C	15	3	3	20	550	1,2,8	12	26
	3 day	12	6	A/C	15	3	3	20	750	1.3	20	20

*IPAP = Inspiratory pressure; EPAP = Expiratory pressure; A/C = Assist Control mode; BACKUP f Backup respiration rate (in A/C mode); BACKUP f Backup respiration rate (in A/C mode); ISENS = Inspiratory sensitivy; ESENS = Expiratory sensitivy; Rise Time = Rise Time setting; Vt = Tidal Volumen; I:E = Ratio of inspiration time to expiration time; Leak = Leak rate; Patients RR = Respiratory rate spontaneous patients.

H1N1 influenza A has also been reported (Intensive-care patients with severe novel influenza A (H1N1) virus infection, 2009)

The findings on the HRCT in these patients show that the role of the initial interstitial lung lesion is that of formulating an early intervention plan that could prevent disease progression, and the further onset of the respiratory complications like the refractory respiratory insufficiency, hypoxemia, and diffuse alveolar damage.

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