ORIGINAL ARTICLE

Pneumonia and Respiratory Failure from Swine-Origin Influenza A (H1N1) in Mexico

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ABSTRACT

BACKGROUND

In late March 2009, an outbreak of a respiratory illness later proved to be caused by novel swine-origin influenza A (H1N1) virus (S-OIV) was identified in Mexico. We describe the clinical and epidemiologic characteristics of persons hospitalized for pneumonia at the national tertiary hospital for respiratory illnesses in Mexico City who had laboratory-confirmed S-OIV infection, also known as swine flu.

METHODS

We used retrospective medical chart reviews to collect data on the hospitalized patients. S-OIV infection was confirmed in specimens with the use of a real-time reverse-transcriptase–polymerase-chain-reaction assay.

RESULTS

From March 24 through April 24, 2009, a total of 18 cases of pneumonia and confirmed S-OIV infection were identified among 98 patients hospitalized for acute respiratory illness at the National Institute of Respiratory Diseases in Mexico City. More than half of the 18 case patients were between 13 and 47 years of age, and only 8 had preexisting medical conditions. For 16 of the 18 patients, this was the first hospitalization for their illness; the other 2 patients were referred from other hospitals. All patients had fever, cough, dyspnea or respiratory distress, increased serum lactate dehydrogenase levels, and bilateral patchy pneumonia. Other common findings were an increased creatine kinase level (in 62% of patients) and lymphopenia (in 61%). Twelve patients required mechanical ventilation, and seven died. Within 7 days after contact with the initial case patients, a mild or moderate influenza-like illness developed in 22 health care workers; they were treated with oseltamivir, and none were hospitalized.

CONCLUSIONS

S-OIV infection can cause severe illness, the acute respiratory distress syndrome, and death in previously healthy persons who are young to middle-aged. None of the secondary infections among health care workers were severe.

In April 2009, the Mexican Secretariat of Health reported an outbreak of respiratory disease. In the affected patients, a novel swine-origin influenza A (H1N1) virus (S-OIV) with molecular features of North American and Eurasian swine, avian, and human influenza viruses[1-4] was found. In the same month, the World Health Organization (WHO) classified the global spread of this virus as a public health event of international concern. After documentation of human-to-human transmission of the virus in at least three countries of two WHO regions, the WHO raised the pandemic level to 6.[5]

As of May 29, 2009, Mexico had reported 4910 confirmed cases and 85 deaths caused by S-OIV.[6] Mexico has reported the greatest number of cases of severe clinical presentations and death,[1] whereas other countries have reported predominantly mild cases of influenza-like illness.

This case series describes the clinical and epidemiologic characteristics of the first 18 persons with pneumonia and laboratory-confirmed S-OIV infection (also known as swine flu) hospitalized at the National Institute of Respiratory Diseases (INER) in Mexico. We also describe apparent transmission of this infection to health care workers during the initial days of the outbreak.

Methods

INER is the Mexican national tertiary care and research center devoted to respiratory diseases. The 178-bed facility provides clinical services primarily for the uninsured population of Mexico City and neighboring states. We retrospectively reviewed medical charts and radiologic and laboratory findings. This study was determined to be exempt from the requirement of institutional review, because it was conducted as part of a public health investigation into retrospective data. All tests and procedures were performed at the request of the physicians in charge of the patients. All study patients had influenza-like illness with opacities found on the chest radiograph (revealing pneumonia) and had laboratory-confirmed S-OIV infection. We also reviewed clinical data from a group of 21 hospitalized patients with influenza-like illness and pneumonia but with a negative result on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing for influenza A (H1N1).

Microbiologic Studies

Nasopharyngeal-swab specimens were collected at admission, and bronchial-aspirate samples were obtained after tracheal intubation. Specimens were placed in transport medium and kept at a temperature from 2 to 4°C. RT-PCR testing was done in accordance with published guidelines from the U.S. Centers for Disease Control and Prevention (CDC).[7] Primers and probes for S-OIV were recently developed and distributed to the Mexican Secretariat of Health and its affiliated national institutions by the CDC. In addition, respiratory specimens from all patients were tested with the use of a multiplex PCR assay for respiratory viral and atypical bacterial panels (Seagene) for the detection of influenza A, influenza B, adenovirus, respiratory syncytial virus, parainfluenza (types 1, 2, and 3), human metapneumovirus, rhinovirus, *Legionella pneumophila*, *Chlamydophila pneumoniae*, and *Mycoplasma pneumoniae*.

Statistical Analysis

Data analysis was conducted using STATA statistical software.[8] We compared clinical characteristics on admission between patients positive for S-OIV who died and those who survived and between patients who were positive for S-OIV and those who were negative for S-OIV. The risk of death was analyzed by means of a univariate Cox proportional-hazards model; odds ratios were calculated and Fisher's exact test was performed for dichotomous categorical variables. Continuous data were tested by means of the Wilcoxon rank-sum test. All reported P values are two-sided and were not adjusted for multiple testing.

Results

Study Patients

The number of emergency room visits for pneumonia or influenza-like illness increased considerably at the INER in Mexico City during the last week of March 2009, peaking in late April and decreasing during the first week of May (Fig. 1). From March 24 through April 24, 2009, a total of 214 emergency room consultations for cases of

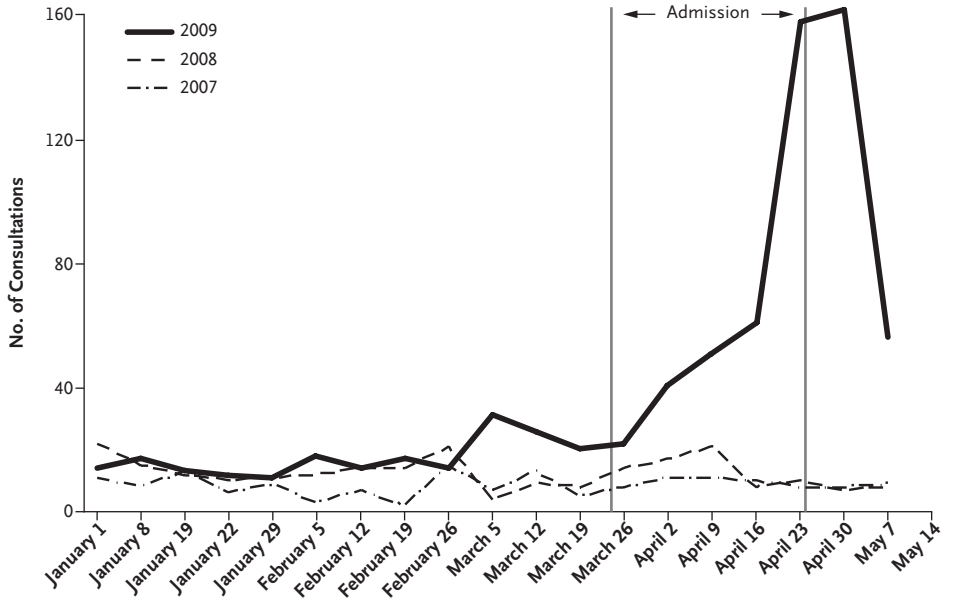

Figure 1. Emergency Room Consultations for Pneumonia or Respiratory Infection, Including Influenza-like Illness, at the National Institute of Respiratory Diseases of Mexico.

Patients with the reported cases were admitted between March 24 and April 24 (gray vertical lines). The Ministry of Health issued an epidemiologic alert on April 17 and a full sanitary alert, with closing of schools and cancellation of many public activities on April 23, after it was confirmed that the patients were infected with the novel influenza A (H1N1) virus.

pneumonia or influenza-like illness were registered, 98 of which required hospitalization. Of these cases, 18 confirmed cases of S-OIV infection, with pneumonia and influenza-like illness, are the focus of this report.

Characteristics of the 18 study patients with confirmed S-OIV infection are listed in Table 1, and Table S1 in the Supplementary Appendix (available with the full text of this article at NEJM.org). The ages of the patients ranged from 9 months to 61 years (median, 38 years). More than half the patients were between 13 and 47 years of age, and 90% were less than 52 years of age. Nine patients (50%) were male.

All patients resided in the Mexico City greater metropolitan area. Eight patients had preexisting medical conditions: arterial hypertension (in three patients), non–type 1 diabetes mellitus (in three, one of whom also had hypertension), asthma (in two), and obstructive sleep apnea (in one). Only three of the patients had undergone seasonal influenza vaccination in 2008–2009; all three survived without requiring mechanical ventilation. None of the patients had a history of pneumococcal vaccination. Among the 14 patients whose occupation was recorded, 6 were students, 2 were taxi drivers, 3 were housekeepers, 1 was a locksmith, 1 was an employee of a billiards parlor, and 1 was a physician who did not have clinical duties and was not an INER employee.

The time between onset of symptoms and admission to the hospital ranged from 4 to 25 days (median, 6) (Fig. 2). All patients had fever, with temperatures higher than 38°C, cough, and dyspnea or respiratory distress. Four of the five children (all under 14 years of age) had diarrhea, and only two patients (11%) reported wheezing. The median Acute Physiology and Chronic Health Evaluation II score[9] was 14 (range, 4 to 32), and the median Sequential Organ Failure Assessment score[10] was 6 (range, 1 to 13); both were higher, indicating more severe abnormalities among the patients who died than among those who lived (Table 2).

Twelve patients sought medical care at other institutions as outpatients before hospitalization at INER and were treated with one or more antibiotics: ceftriaxone (five patients), amikacin (three),

azithromycin (one), amoxicillin–clavulanate (two) or other macrolides (three), or another agent (two). Except for two patients transferred from other health centers, the reported hospitalization was the first hospitalization related to the disease.

LABORATORY RESULTS

At the time of admission, all 16 tested patients had elevated lactate dehydrogenase levels; levels in 10 patients exceeded 1000 IU per liter (range, 1086 to 6309). Ten of the 16 patients had increased creatine kinase levels, which were above 1000 IU per liter (range, 1099 to 5122) in 5 patients. Eleven of all 18 patients (61%) had lymphopenia (<1000 lymphocytes per cubic millimeter), 2 patients had more than 10,000 leukocytes per cubic millimeter, and 2 patients had mild thrombocytopenia at admission. Patient 3 had myocardial ischemia, as revealed on electrocardiography, with myocardial infarction documented on autopsy. Three patients had elevated creatinine levels (1.8 to 4.6 mg per deciliter [159 to 407 μmol per liter]) at admission. Four patients had D-dimer levels greater than 1000 IU per liter, and 11 patients had elevated aminotransferase levels (aspartate aminotransferase, 50 to 65 U per liter; alanine aminotransferase, 43 to 147 U per liter). Results of other routine tests were within normal limits.

The following bacterial cultures obtained within 24 hours after admission were negative: cultures of blood specimens from six patients, of bronchial aspirate samples from two patients, and of pleural-fluid specimens from one patient. Three of these patients had received antibiotics within 24 to 48 hours before admission. No other respiratory viruses or atypical bacteria were identified by means of PCR assay in any patient tested.

All 18 patients had radiologically confirmed pneumonia (Fig. 3A, and Fig. S2 and S3 in the Supplementary Appendix) with bilateral patchy alveolar opacities (predominantly basal), affecting three or four lung quadrants in 11 patients. Also common were linear, reticular, or nodular shadows (interstitial opacities). Findings on chest radiographs were consistent with the acute respiratory distress syndrome in all patients requiring mechanical ventilation.[11]

TREATMENT

None of the patients had received oseltamivir before admission; 14 received it in the hospital, at a dose of 75 mg twice a day for a minimum of 5 days; 11 began receiving it at admission (a mean of 8 days after the onset of symptoms) and 3 between 2 and 10 days after admission. Four patients who survived did not receive oseltamivir. After admission, 17 patients received ceftriaxone and 10 received clarithromycin. Additional antibiotics were prescribed in several patients, on the basis of their clinical course: three were given levofloxacin; seven, vancomycin; five, cefepime; five, imipenem; and two, dicloxacillin.

CLINICAL COURSE DURING HOSPITAL STAY

Respiratory distress requiring intubation and mechanical ventilation developed in 10 patients within the first 24 hours after admission. These patients had a median oxygen saturation of 71% (interquartile range, 64 to 77) in the absence of supplementary oxygen (2240 m above sea level), and treatment of eight patients involved positive end-expiratory pressure at or above 16 cm of water. Two additional patients required mechanical ventilation during their stay in the hospital (Table S2 in the Supplementary Appendix). Duration of mechanical ventilation ranged from 7 to 30 days in patients who survived and from 4 to 17 days in patients who died. Norepinephrine infusion was begun in 9 of 18 patients (50%) during the period of hospitalization, and 5 patients received corticosteroids (hydrocortisone at a dose of 300 mg per day or methylprednisolone at a dose of 60 mg per day). Of the six patients in whom renal failure developed, five died. Seven patients had multiorgan system failure. None of the patients had disseminated intravascular coagulation or neurologic complications. Four patients had ventilator-associated pneumonia, each case with a different cause: *Acinetobacter baumannii*, *Achromobacter xylosoxidans*, methicillin-resistant *Staphylococcus aureus*, or *Escherichia coli*.

Of the 18 patients, 7 died, and 11 recovered and were discharged from the hospital. Patients died within 10 to 23 days (mean, 14) after the onset of illness and between 4 and 18 days (mean, 9 days) after admission. Figure 3B shows a lung-tissue specimen from the autopsy of Patient 3, a 43-year-old patient who died after a 14-day illness complicated by acute renal failure and myocardial infarction. Pathological evaluation of the lung showed diffuse alveolar damage, thick hyaline membranes, and prominent fibroblast proliferation.

Patients with confirmed S-OIV infection had more severe disease, including a higher death rate (Table S2 in the Supplementary Appendix), than did hospitalized patients with negative test results. The median time from illness onset to collection of samples for viral testing was 9 days (range, 3 to 46) among the 18 patients who were positive for S-OIV infection and 10 days (range, 3 to 27) among those with negative test results (P=0.50).

CLINICAL INFECTION IN CONTACTS AND HEALTH CARE WORKERS

Patients identified a total of 82 family contacts, 20 of whom had respiratory symptoms within a week after the patient was hospitalized. Of the 20, 4 required hospitalization, including 3 contacts of Patient 6; 1 contact who had Down's syndrome died in another hospital from respiratory failure. Patient 2, in whom severe respiratory fail-

Table 1. Characteristics of the 18 Study Patients Who Had Confirmed Infection with Novel Swine-Origin Influenza A (H1N1) Virus.*

Variable	Value
Male sex — no./total no. (%)	9/18 (50)
Age — yr	
Median	38
Range	0.75–61
All patients — no./total no. (%)	
≤5 yr	3/18 (17)
>5 to ≤10 yr	1/18 (6)
>10 to ≤15 yr	1/18 (6)
>15 to ≤50 yr	11/18 (61)
>50 yr	2/18 (11)
Patients who died — no./total no.	
≤5 yr	0/3
>5 to ≤10 yr	1/1
>10 to ≤15 yr	1/1
>15 to ≤50 yr	4/11
>50 yr	1/2
Symptom or outcome — no./total no. (%)	
Cough	18/18 (100)
Blood in sputum	6/18 (33)
Rhinorrhea	5/18 (28)
Wheezing	2/18 (11)
Headache	4/18 (22)
Myalgia or arthralgia	8/18 (44)
Fever (temperature >38°C)	18/18 (100)
Dyspnea or respiratory distress	18/18 (100)
Diarrhea	4/18 (22)
Sudden onset of symptoms	13/18 (72)
Hypotension that did not resolve after fluid administration	9/18 (50)
Mechanical ventilation on admission	10/18 (56)
Death	7/18 (39)

Table 1. (Continued.)

Variable	Value
Days from onset of symptoms to emergency room — median (range)	6 (4–13)
Days from onset of symptoms to death — median (range)	14 (10–23)
Days from admission to death — median (range)	9 (4–18)
Laboratory findings — median (range)	
Leukocyte count — per mm³	6000 (3100–22,200)
Lymphocyte count — per mm³	850 (200–3700)
Serum creatine kinase — U/liter	366 (58–2156)
Serum lactate dehydrogenase — U/liter	1226 (594–3871)
Abnormal finding — no./total no. (%)	
Lymphocyte count <1000 per mm³	11/18 (61)
Creatine kinase >240 U/liter	10/16 (62)
Lactate dehydrogenase >350 U/liter	16/16 (100)

* Coexisting conditions were type 2 diabetes, asthma, high blood pressure, and the obstructive sleep apnea syndrome, as described in the Supplementary Appendix.

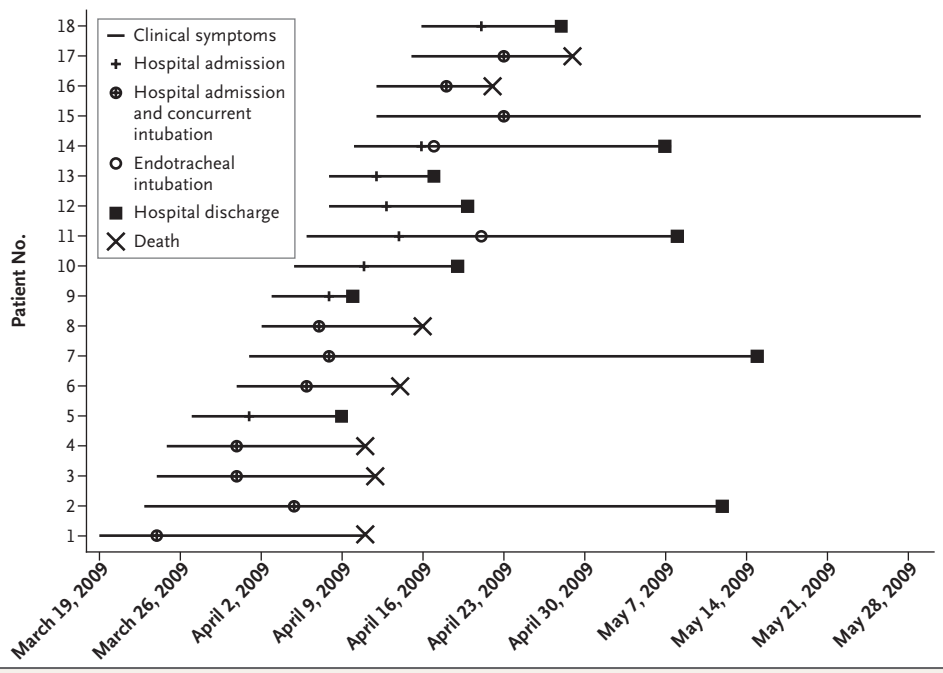

Figure 2. Clinical Courses of the Study Patients.

The median time of presentation to the hospital was 6 days after the onset of symptoms. Most deaths occurred in patients who required mechanical ventilation on admission. Patient 15 was discharged from the hospital on June 8, 2009.

Table 2. Survival and Death among the 18 Study Patients Who Had Confirmed Infection with Novel Swine-Origin Influenza A (H1N1) Virus.*

Variable at Admission	Patients Who Survived (N=11)	Patients Who Died (N=7)	Hazard Ratio or Odds Ratio for Death (95% CI)	P Value
Age — yr				0.81
Median	37	45	1.00	
Range	0.75–61	9–52	0.96–1.04	
Male sex — no./total no.	4/11	5/7	2.2 (0.4–11.5)	0.34
Hypotension that did not resolve after fluid administration — no./total no.	2/11	7/7		0.02
Orotracheal intubation required within first 24 hr after admission — no./total no.	3/11	7/7		0.06
Renal failure any time during follow-up — no./total no.	1/11	5/7	25 (1.3–1295)	0.01
Coexisting condition — no./total no.†	5/11	3/7	0.78 (0.2–3.6)	0.75
Days from illness onset to admission				0.20
Median	6	6	0.71	
Range	4–13	5–8	0.4–1.2	
Lactate dehydrogenase — U/liter				0.40
Median	1086	2032	1.00	
Range	594–2429	690–3871	0.99–1.01	
Creatine kinase — U/liter				0.45
Median	189	514	1.00	
Range	58–1249	175–2156	0.99–1.01	
Lymphocyte count per mm^3				0.25
Median	1000	400	0.99	
Range	500–3700	200–1300	0.98–1.00	
PaO_2 — mm Hg				0.44
Median	55.4	41.5	0.96	
Range	33.7–70.1	39.0–51.0	0.89–1.04	
$PaCO_2$ — mm Hg				0.91
Median	28.7	36	0.99	
Range	23.7–61.7	15–66	0.94–1.05	
pH				0.02
Median	7.42	7.35	3.19×10^{-12}	
Range	7.38–7.93	7.19–7.43	3.43×10^{-22}–0.29	
Initial PaO_2:FIO_2				0.71
Median	231	197	0.99	
Range	22–334	186–243	0.98–1.01	
Acute respiratory distress syndrome — no./total no.	3/10	4/7	1.18 (0.26–5.33)	0.82
APACHE II score				0.02
Median	11	19	1.20	
Range	4–20	14–32	1.03–1.40	

Table 2. (Continued.)

Variable at Admission	Patients Who Survived (N=11)	Patients Who Died (N=7)	Hazard Ratio or Odds Ratio for Death (95% CI)	P Value
SOFA score				0.05
Median	3.5	11	1.31	
Range	1–13	5–12	1.00–1.71	
PaO_2:FiO_2 on oxygen or mechanical ventilation				0.02
Median	164	53	0.95	
Range	87–250	46–107	0.91–0.99	
Opacity in 3 or 4 lung quadrants in initial radiograph — no./total no.	7/11	4/7	1.76 (0.37–8.29)	0.47
Use of antibiotics before admission — no./total no.	9/11	4/7	0.48 (0.10–2.20)	0.34
Use of corticosteroids — no./total no.‡				
Before admission	1/11	1/7	0.67 (0.08–5.71)	0.72
During hospitalization	2/11	3/7	3.37 (0.25–52.34)	0.32

* Hazard ratios or odds ratios for continuous variables are given for a 1-unit increase. Unless otherwise noted, hazard ratios were calculated, and these and the P values were estimated using a univariate Cox regression. P values are two-tailed and were not adjusted for multiple comparisons. A multivariable Cox regression analysis was not attempted because of the small number of patients. For variables that did not meet the assumptions of the proportional-hazards model — hypotension that did not resolve after fluid administration and the requirement of orotracheal intubation in the first 24 hours after admission — P values were obtained with the use of the log-rank test. For renal failure any time during follow-up and use of corticosteroids during hospitalization, odds ratios were calculated, and P values were obtained with the use of Fisher's exact test. The Acute Physiology and Chronic Health Evaluation (APACHE) II score can range from 0 to 71, with increasing scores reflecting more severe dysfunction.[9] The partial pressure of arterial oxygen (PaO_2), partial pressure of arterial carbon dioxide ($PaCO_2$), pH, and the ratio of PaO_2 to the fraction of inspired oxygen (FiO_2) were measured while the patients were breathing ambient air, except for two patients, who were breathing oxygen (see the Supplementary Appendix). The Sequential Organ Failure Assessment (SOFA) organ system score was ascertained for three organ systems, with a range for each system of 0 to 4 and a higher score indicating more severe dysfunction.[10]

† Coexisting conditions were type 2 diabetes mellitus, asthma, high blood pressure, and the obstructive sleep apnea syndrome, as described in the Supplementary Appendix.

‡ Corticosteroids were administered at the discretion of the attending physicians. None of the patients were given oseltamivir during the first 48 hours after the onset of symptoms.

ure developed, is the mother of Patient 9, who had milder disease and received early treatment with oseltamivir.

Influenza-like illness or respiratory symptoms developed in 22 of 190 health care workers caring for the first three patients with confirmed S-OIV infection in the emergency room and the intensive care unit, including 19 of 104 workers who were within 2 m of a patient or had direct contact. These 22 workers received oseltamivir for 5 days and were sent home for 3 to 7 days. They had mild-to-moderate disease, and none required hospitalization. Three of the 22 workers, who were nurses in the emergency room, had nasopharyngeal-aspirate samples that were positive for S-OIV. After infection-control measures were strictly enforced — with patients confined and isolated in three hospital areas and N95 respirators used in addition to goggles, gowns, and gloves, as well as liberal use of gel-alcohol hand sanitizer — no more health care workers had influenza-like illness, although 26 additional workers received oseltamivir for 5 days because of varied respiratory symptoms.

DISCUSSION

This case series of the first 18 patients hospitalized in Mexico City with S-OIV infection documents the clinical findings of severe illness or death associated with S-OIV infection that were seen during the beginning of the S-OIV pandemic. The patients, most of them previously healthy, had an influenza-like illness that progressed during a period of 5 to 7 days, had pneumonia, and had findings during the first day of hospital ad-

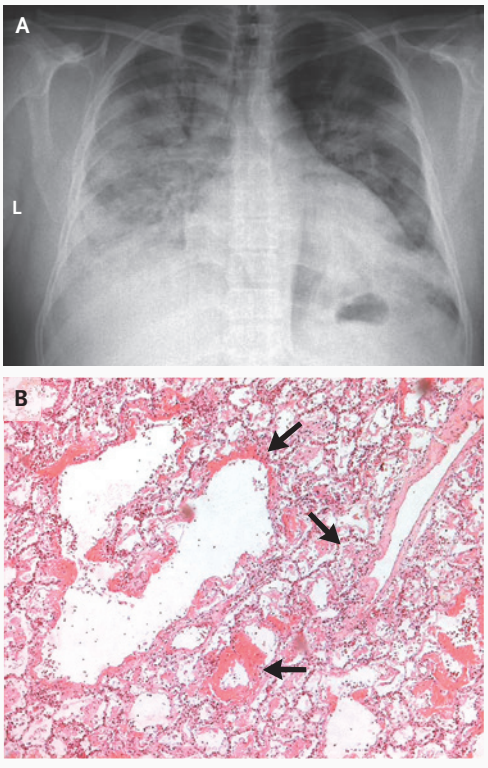

Figure 3. Initial Radiograph of the Lung and Lung-Tissue Sample from Patient 3.

The radiograph (Panel A) shows bilateral alveolar opacities in the base of both lungs that progressed and became confluent. The specimen (Panel B, hematoxylin and eosin) shows necrosis of bronchiolar walls (top arrow), a neutrophilic infiltrate (middle arrow), and diffuse alveolar damage with prominent hyaline membranes (bottom arrow). Bacterial cultures were negative on admission, and no evidence of bacterial infection of the lungs was found. The patient ultimately died.

mission that fulfilled the criteria of acute lung injury or the acute respiratory distress syndrome.[12] Seven patients died, all from multiorgan system failure. The most consistent laboratory characteristics were increased lactate dehydrogenase level, a total leukocyte count within normal limits, lymphopenia,[13] and increased creatine kinase level, most likely due to myositis (or myocardial ischemia, in one patient).

The patients described were part of an epidemic of influenza-like illness with pneumonia seen at our institution and other Mexican hospitals, and only a fraction of them tested positive for S-OIV. A false negative test in patients who had infection with S-OIV would be more likely if the test were delayed or if patients had limited viral shedding. In general, patients who tested negative for S-OIV had a milder clinical course than those who tested positive but were as much a part of the burden of the epidemic as those who were not tested.

Risk factors for severe S-OIV illness are still unknown, but most of our patients were young to middle-aged and had previously been healthy. The majority of the S-OIV infections reported in other countries have been mild, influenza-like illnesses.[2] Mexico has also reported a large number of persons with mild disease, through the national surveillance system for influenza, but the full spectrum of clinical illness has not been determined. Other countries will probably report more severe infections as the pandemic spreads and the number of infected persons increases. One contributing factor for death in our patients may have been delayed admission and delayed initiation of oseltamivir. For seasonal influenza, the elderly and young children are at higher risk for severe disease; however, more than half of our patients were between 13 and 47 years of age, which was similar to the age distribution reported in national data of H1N1 infections in Mexico.[6] During the 1918 pandemic, a large number of deaths were associated with bacterial infection,[14] but concurrent bacterial infection does not appear to be a major contributing factor to the severity of illness in our patients, possibly in part because most received antibiotics before hospitalization.

Mortality among the patients requiring mechanical ventilation was 58%, and although four patients had nosocomial pneumonia, in most of our patients, lung damage was most likely due to the primary effect of infection with influenza virus. Possible mechanisms of damage include direct injury to the respiratory epithelium[15] with a secondary cytokine storm. We do not currently know whether our patients, especially those who died, had viremia, as was reported in association with H5N1 infection, a very aggressive variety of influenza.[13,16-18] Coinfection with other respiratory viruses could also explain the increased pathogenicity among our patients[19,20]; however, no other common respiratory viruses were found in our patients. Only three of the patients had received influenza vaccine in fall 2009, since most patients were within the age groups for which vaccine was not recommended in Mexico. It is currently unknown whether seasonal vaccination

offered any protection against S-OIV infection, however. We did not find a factor that, before the onset of illness, predicted a worse outcome or death among our patients.

Since 2000, the WHO has prompted countries to prepare for a potential influenza pandemic. In Mexico, pandemic influenza planning began in 2001. Activities included the introduction of yearly influenza vaccination and a program to develop the country's national vaccine production. In 2006, a strategic reserve of oseltamivir, antibiotics, and protective items for health care personnel was established. This reserve is the source of the oseltamivir prescribed to our patients and to most hospitalized patients in Mexico. The experience in our institution highlights the need to reinforce precautions and use of personal protective equipment to prevent the infection of health care workers.

In conclusion, S-OIV infection can cause serious illness and death in young, previously healthy persons. Future studies should identify predictive factors for severe disease and, especially, the effectiveness of early oseltamivir treatment and protection offered by having undergone seasonal influenza vaccination.

No potential conflict of interest relevant to this article was reported.

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APPENDIX

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