

Pneumonia in patients with novel influenza A (H1N1) virus in Southeastern Turkey

Tacettin Örnek¹, Funda Demirtaş Yalçın², Selami Ekin², Şaban Yalçın³, Mücahit Yemişen⁴

¹Zonguldak Karaelmas University Medical Faculty, Department of Pulmonology, Zonguldak, Turkey

²Şanlıurfa Education and Research Hospital, Clinic of Chest Diseases, Şanlıurfa, Turkey

³Harran University Medical Faculty, Department of Anaesthesiology and Reanimation, Şanlıurfa, Turkey

⁴Clinic of Infectious Diseases, Şanlıurfa Balıklıgöl State Hospital, Şanlıurfa, Turkey

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Pneumonie bei Patienten mit einer Infektion mit dem neuen Influenza A (H1N1) Virus in der Südost-Türkei

Zusammenfassung. Ziel dieser Studie war es, die klinischen Charakteristika, sowie die Röntgen- und Laborbefunde von hospitalisierten Patienten mit einer neuen, labormäßig gesicherten, Infektion mit dem Schweinegrippe Influenza A Virus (S-OIV) mit Pneumonie zu beschreiben.

Es wurden 56 zwischen Oktober und Dezember 2009 wegen einer Pneumonie stationär aufgenommene Patienten, die auf S-OIV getestet worden waren, retrospektiv ausgewertet. 33 dieser Patienten hatten einen positiven Befund. Sie wurden mit den 23 Patienten mit negativem Befund verglichen.

Die Mortalität der Patienten mit positivem Befund lag bei 24,2%. Von den 33 Patienten hatten 42,4% zumindest eine zugrunde liegende Erkrankung und 4 (12%) Patientinnen waren schwanger oder post partum. 14 der Patienten mit S-OIV Infektion wurden in einer Intensivstation behandelt. Das häufigste Symptom war Atemnot. Die mittlere Spitzen - Körpertemperatur während des stationären Aufenthaltes war in dieser Gruppe mit $39,42 \pm 0,70$ Grad Celsius höher als in der Gruppe mit negativem S-OIV Befund ($38,51 \pm 1,05$) ($p=0,001$). Auch die Thrombozytopenie sowie der Anstieg der Creatin-Kinase und der Laktatdehydrogenase waren statistisch signifikant ausgeprägter. Bei den Patienten mit S-OIV Infektion war eine bilaterale Infiltration im Vergleich häufiger.

Obwohl sich manche klinischen Daten und Röntgen- sowie Laborbefunde der Patienten mit S-OIV Infektion von den bei S-OIV negativen Patienten erhobenen Befunden signifikant unterschieden, sollten unseres Er-

achtens alle Patienten mit einer Pneumonie während einer Pandemie auf Influenza A getestet werden.

Summary. The objective of this study was to describe the clinical characteristics and the radiological and laboratory findings of the hospitalised patients who had novel, laboratory-confirmed, swine-origin influenza A virus (S-OIV) infection with pneumonia.

Between October and December 2009, 56 patients hospitalised for pneumonia who were tested for S-OIV infection were retrospectively evaluated. Thirty-three patients had positive S-OIV infections. In addition, 23 of the 56 patients who had negative test results for S-OIV infection were compared with the positive group.

The mortality rate amongst the patients with S-OIV infection was 24.2%. Of the 33 patients, 42.4% had at least one underlying medical condition and 4 (12%) patients were pregnant or postpartum. Fourteen patients (42.4%) with S-OIV infection were followed up in an intensive care unit. The most common symptom was dyspnea. The mean peak body temperature during hospital stay (39.42 ± 0.70) was higher in this group than in the negative group (38.51 ± 1.05) ($p=0.001$). Thrombocytopenia, increased creatine kinase and elevated lactate dehydrogenase levels were statistically significant. Bilateral infiltration was more common in the patients with S-OIV infection.

Although some laboratory, radiological and clinical data show a significant difference between the patients with S-OIV pneumonia and the negative group, each patient presenting with signs of pneumonia during pandemic should be tested for Influenza A.

Key words: H1N1 virus, hospitalisation, infection, influenza A virus, pneumonia.

Introduction

Swine influenza (H1N1) is a novel influenza A virus comprising a reassortment of four distinct genetic elements,

Correspondence: Dr. Tacettin Örnek, Zonguldak Karaelmas University Medical Faculty, Department of Pulmonology, 67600 Zonguldak, Turkey,
 E-mail: tacettinornek@yahoo.com

swine, human, avian, and Eurasian swine genetic components, which combine to form a single influenza virus [1]. The first human infections with the new swine-origin influenza A virus (S-OIV) were confirmed in April 2009 in Mexico and the United States. Since then, Turkey and several other countries experienced outbreaks of respiratory illness caused by S-OIV. On 11 June 2009, WHO announced a global 2009 influenza pandemic [2]. On 16 May 2009, the first infection by S-OIV in Turkey was reported. Outbreak spread throughout the country during the winter wave; the first death due to S-OIV infection in Turkey occurred on 24 October 2009.

Previous studies have reported that a prominent clinical feature of S-OIV infection is severe pneumonia [3–5]. In this report, we aim to describe the clinical characteristics and the radiological and laboratory findings of patients with H1N1 virus pneumonia who lived in the southeastern region of Turkey. Attempts to define specific clinical or laboratory parameters to distinguish S-OIV from other types of pneumonia might facilitate early suspicion of S-OIV infection.

Methods

This study was performed at Şanlıurfa Education and Research Hospital, which is located in the southeastern region of Turkey. We retrospectively reviewed medical charts and radiological and laboratory findings of the patients who were followed up at the hospital between 27 October 2009 and 26 December 2009. We enrolled all hospitalised patients with pneumonia for whom nasopharyngeal swab specimens were collected due to suspected S-OIV infection. We separated the patients into two groups. In the positive group, 33 patients had laboratory-confirmed S-OIV infection. Twenty-three patients without an S-OIV infection (confirmed by laboratory tests) were used to document the differences between the patients with or without S-OIV infection.

Microbiological studies

Nasopharyngeal swab specimens were collected upon admission and kept at a temperature ranging from 4 to 8°C. Specimens were sent to a Turkish government health ministry laboratory centre called “Refik Saydam Hıfızısıhha Center Presidency” (RSHCP). Specimens were tested using real-time reverse-transcriptase-polymerase-chain-reaction (rRT-PCR), in accordance with the guidelines provided by the WHO. At the national influenza centre of RSHCP, diagnosis of influenza and viruses-forming influenza-like illness was achieved using primers and probe sequence provided by the U.S. Centers for Disease Control (CDC) [6].

Statistical analysis

Data analysis was conducted using SPSS 11.5 statistical software. Continuous variables were summarised as means (\pm SD) or medians (with interquartile ranges). A *P* value of less than 0.05 was considered statistically significant. Mann-Whitney *U*-test, Chi-square test, or Fisher’s exact test was used as appropriate. All values were two-sided.

Results

Demographic characteristics of the patients with S-OIV infection are shown in Table 1. The minimum and maximum

Table 1. Characteristics of the patients with pneumonia who had S-OIV infection

Variable	Value
Gender – no (%)	
Male	20 (60.6)
Female	13 (39.4)
Age – year	
Median	30
Range	13–70
Occupation – no (%)	
Housewife	12 (36.4)
Unemployed	8 (24.2)
Freelancer	5 (15.2)
Farmer	4 (12.1)
Comorbidities – no (%)*	14 (42.42)
Hospital stay – in days	
Mean	6.42 \pm 4.56
Range	1–24
ICU stay – in days	
Mean	6.0 \pm 6.0
Range	1–24
Duration of symptoms onset to admission – in days	
Mean	4.3 \pm 2.31
Range	2–10

*The number of patients who had at least one comorbidity.

ages of the positive group were 13 and 70 years, respectively, with a median age of 30 years. The median age of the negative group was 34 years, with a range of 15–80 years; 57.6% of the positive group and 69.6% of the negative group had no comorbidities. In the positive group, 9 of 33 patients had pulmonary disease, such as chronic obstructive pulmonary disease (COPD) or asthma, 3 patients were pregnant, 2 patients had type 2 diabetes mellitus and 1 patient was postpartum. Other comorbidities in the positive group were Down syndrome ($n=1$), hypertension ($n=1$) and congestive heart failure ($n=1$). There were no pregnant or postpartum patients in the negative group, and 4 of 23 patients had pulmonary disease, such as chronic obstructive pulmonary disease (COPD) or asthma.

Fourteen patients (42.4%) in the positive group and 8 patients (34.8%) in the negative group were followed up in the intensive care unit (ICU). The duration of hospital

Table 2. Comparison of the symptoms during admission in the positive group and negative groups

Symptom	Positive group <i>n</i> (%)	Negative group <i>n</i> (%)	<i>p</i> *
Dyspnoea	32 (97.0)	17 (73.9)	0.015
Cough	31 (93.9)	22 (95.7)	1
Sputum	25 (75.8)	19 (82.6)	0.743
Hemoptysis	6 (18.2)	2 (8.87)	0.449
Fever	32 (97.0)	20 (87.0)	0.295
Runny nose	17 (51.5)	9 (39.1)	0.361
Headache	26 (78.8)	18 (78.3)	0.962
Sore throat	27 (81.8)	13 (56.5)	0.039
Myalgia	29 (87.9)	19 (82.6)	0.704

*Pearson chi-squared test and Fisher’s exact test were performed.

stay (6.42 ± 4.56 days) and ICU stay (6.0 ± 6.0) in the positive group was lower than in the negative group (8.0 ± 5.50 days, 7.37 ± 7.55 days, respectively), but this difference was not statistically significant ($p=0.296$ and 0.810 , respectively).

A comparison of the symptoms between the groups during admission is shown in Table 2. The most common symptom was dyspnea in the positive group. Dyspnea and sore throat were more common in the positive group ($p=0.015$ and 0.039 , respectively).

In auscultation, crackles were identified in 63.6% ($n=21$) of the positive group. 54.5% of the crackles were bilateral. Cyanosis and mental confusion were seen more frequently in the positive group ($n=11$, 33.3% and $n=15$, 45.5%, respectively) than in the negative group ($n=3$, 13.0% and $n=7$, 30.4%, respectively) but this difference was not statistically significant ($p=0.258$ and 0.120 , respectively). The mean highest body temperature during the hospital stay of the positive group (39.42 ± 0.70) was higher than that of the negative group (38.51 ± 1.05) ($p=0.001$).

Table 3. Frequency of MV, ARDS and exitus in both groups

	Positive group <i>n</i> (%)	Negative group <i>n</i> (%)	<i>p</i> *
MV	8 (24.2)	3 (13.0)	0.496
ARDS	7 (21.2)	4 (17.4)	1
Exitus	8 (24.2)	2 (8.7)	0.172

*Fisher's exact test was performed.

The frequency of mechanical ventilation (MV), Acute Respiratory Distress Syndrome (ARDS) and death was higher than in the negative group, but this difference was not statistically significant ($p=0.496$, 1 and 0.172 , respectively) (Table 3). Neither patients in the positive group with ARDS nor those who underwent MV survived.

Laboratory results

A complete blood cell count was performed on all 33 patients and on the negative group. The results of the blood

Table 4. Laboratory findings of the patients with S-OIV infection and negative group*

Variable	Positive group	Negative group	<i>p</i> **
Hemoglobin			
Mean value in patients with anemia	10.96 ± 1.0	10.12 ± 1.49	
Anemia – no (%)	11 (33.3)	6 (26.1)	0.562
Leucocyte count			
Mean count in patients with leucocytosis – cells/mm ³	$19,458 \pm 14,132$	$17,433 \pm 7,484$	
Leucocytosis – no (%)	12 (36.4)	12 (52.2)	0.240
Lymphocyte count			
Mean count in patients with lymphopenia – cells/mm ³	600.0 ± 209.8	600.0 ± 238.1	
Lymphopenia – no (%)	11 (33.3)	7 (30.4)	0.819
Platelet count			
Mean count in patients with thrombocytopenia – cells/mm ³	$108,285 \pm 31,555$	$131,500 \pm 20,506$	
Thrombocytopenia – no (%)	14 (42.4)	2 (8.7)	0.007
Alanine aminotransferase (ALT)			
Mean value in patients with elevated ALT – U/l	99.4 ± 71.56	99.24 ± 29.90	
Elevated ALT – no (%)	5 (15.6)	7 (30.4)	0.190
Aspartate aminotransferase (AST)			
Mean value in patients with elevated AST – U/l	72.68 ± 52.37	90.69 ± 58.72	
Elevated AST – no (%)	16 (50)	11 (47.8)	0.874
Gamma-glutamyl transpeptidase (GGT)			
Mean value in patients with elevated GGT – U/l	124.89 ± 61.27	113.49 ± 71.48	
Elevated GGT – no (%)	9 (31)	6 (27.3)	0.770
Lactate dehydrogenase (LDH)			
Mean value in patients with elevated LDH – U/l	649.68 ± 421.47	680.0 ± 325.97	
Elevated LDH – no (%)	28 (90.3)	13 (61.9)	0.019
Creatine kinase (CK)			
Mean value in patients with elevated CK – U/l	516.47 ± 409.84	586.28 ± 527.75	
Elevated CK – no (%)	15 (60)	5 (23.8)	0.014
Serum creatinin			
Mean value in patients with elevated serum creatinin – mg/dl	1.77 ± 0.32	–	
Elevated serum creatinin – no (%)	2 (6.3)	0 (0)	0.504
Blood urea			
Mean value in patients with elevated blood urea – mg/dl	68.88 ± 13.45	69.33 ± 11.72	
Elevated blood urea – no (%)	5 (15.6)	3 (13.0)	1
C-reactive protein (CRP)			
Mean value in patients with positive CRP – mg/l	17.65 ± 10.43	18.18 ± 10.72	
Positive CRP – no (%)	13 (61.9)	8 (50)	0.469

*Plus-minus values are means \pm SD; **Pearson chi-squared test and Fisher's exact test were performed.

cell count and other biochemical parameters are shown in Table 4. Thrombocytopenia, increased creatine kinase and elevated lactate dehydrogenase levels were observed in the patients with S-OIV infection ($p=0.007$, 0.014 and 0.019 , respectively). The mean value of platelet count was 202.575 ± 129.600 and 283.608 ± 133.290 in the positive group and negative group, respectively ($p=0.002$). The mean value of creatine kinase and serum creatinin was higher in the positive group (337.40 ± 385.14 and 0.82 ± 0.31 , respectively) than in the negative group (191.89 ± 327.63 and 0.67 ± 0.19 , respectively) ($p=0.033$ and 0.026 , respectively).

The mean arterial PO_2 of the patients with S-OIV and the S-OIV negative group was 50.5 ± 8.81 ($n=11$) and 56.8 ± 11.06 ($n=6$), respectively ($p=0.262$). The mean pH of arterial blood was 7.34 ± 0.06 ($n=11$) and 7.34 ± 0.18 ($n=6$) in the positive group and negative group, respectively ($p=0.288$).

In 11 patients with S-OIV infection, bacterial cultures of sputum or bronchial aspirate samples were obtained during the hospital stay. Specimens were negative, with the exception of two samples, which were positive for *Pseudomonas aeruginosa*. Each of the blood specimen cultures taken from 10 patients was negative. Each of the blood specimen cultures, bronchial aspirate samples or bacterial cultures of sputum taken from 11 of 23 patients belonging to the negative group was also negative.

Radiology

All patients had opacities on a chest radiograph. Bilateral infiltration was seen more frequently in the patients with S-OIV infection ($n=19$, 57.6%) as compared to the negative group ($n=7$, 30.4%) ($p=0.044$). In 27.3% ($n=9$) of the positive group, bilateral expansive infiltration on upper, medial and lower zones was observed, but there were no patients in whom infiltration extended throughout the lung zones in the negative group ($p=0.007$). Pneumothorax and pleural effusion were seen in two different patients.

Treatment

All of the patients received oseltamivir upon admission, at a dose of 75 mg twice a day. Oseltamivir treatment was maintained for 5 days in the patients with S-OIV infection, but in the negative group, the duration of oseltamivir treatment was limited by the time required to obtain negative laboratory test results for S-OIV. After admission, 17 patients with S-OIV received ceftriaxone and others received ceftriaxone combined with other antibiotics (13 received clarithromycin, 1 received levofloxacin, 1 received moxifloxacin). Other initial treatments were imipenem or meropenem for 7 patients (one combined with vancomycin), moxifloxacin for 2 patients, piperacillin-tazobactam combined with ciprofloxacin for 2 patients, sulbactam-ampicillin for 2 patients, ceftazolin sodium for 2 patients and sulbactam-cefoperazon for 1 patient. Additional antibiotics were prescribed for several patients, on the basis of their clinical course: four were given imipenem or meropenem (combined with vancomycin in two patients); one,

piperacillin-tazobactam + vancomycin and one, sulbactam-cefoperazon + vancomycin.

Discussion

We describe the clinical, radiological and laboratory features of pneumonia that developed in the patients with S-OIV infection. The most common symptom was dyspnea. The mean peak body temperature during hospital stay amongst patients with S-OIV infection was higher than in the negative group ($p=0.001$). Thrombocytopenia, increased creatine kinase and elevated lactate dehydrogenase levels were observed in the patients with S-OIV infection. Bilateral infiltration was seen more frequently in the patients with S-OIV infection ($p=0.044$).

Swine influenza pneumonia was seen in 66% of hospitalised patients with S-OIV infection [7]. This number varied in some studies [3, 8–12], as did the number of hospitalised patients associated with patient characteristics.

All of the patients were living in the Şanlıurfa province of Turkey and were followed at Şanlıurfa Education and Research Hospital, located in the southeastern region of Turkey. The mean age of the patients with swine influenza pneumonia was lesser than the patients with community-acquired pneumonia. The frequency of comorbidity in the patients with swine influenza pneumonia was similar to that reported by Perez-Padilla et al. [4]. Most of the studies suggest that some younger and healthy people, especially middle-aged adults and pregnant women, were severely affected by S-OIV infection [3–5, 13–16]. One study showed that the new H1N1 virus causes pneumonia in ferrets, which is moderate in severity compared to that caused by seasonal H1N1 virus [17]. If we assume that the severity is the same as observed for patients admitted to the ICU in our study, there is no difference between healthy and comorbid patients with regard to severity. Extremes in age and multiple and debilitating underlying medical conditions might be contributing to the severity of illness in these patients.

Primary viral pneumonia is the most common finding in the patients with severe S-OIV infection [11]. The onset of swine influenza pneumonia is often abrupt. In adults with S-OIV, pneumonia presents as an influenza-like illness with a temperature higher than 39°C (102°F) accompanied by prominent myalgia [1]. The most consistent symptoms were cough, sore throat, sputum, dyspnea and fever that varied in different studies [4, 13, 18, 19]. In our study, dyspnea and sore throat were most common in swine influenza pneumonia.

The most consistent laboratory characteristics in our patients with S-OIV infection were thrombocytopenia, increased creatine kinase and elevated lactate dehydrogenase levels. Venkata et al. [20] demonstrated that thrombocytopenia was common in ICU patients. In the reports from Chile [21] and Italy [12], 20% and 27% of the patients with S-OIV had thrombocytopenia, respectively. More commonly reported in children, myositis associated with influenza A and B has been well documented and appears to occur most often during the convalescent phase of illness [22]. The elevation of lactate dehydrogenase and

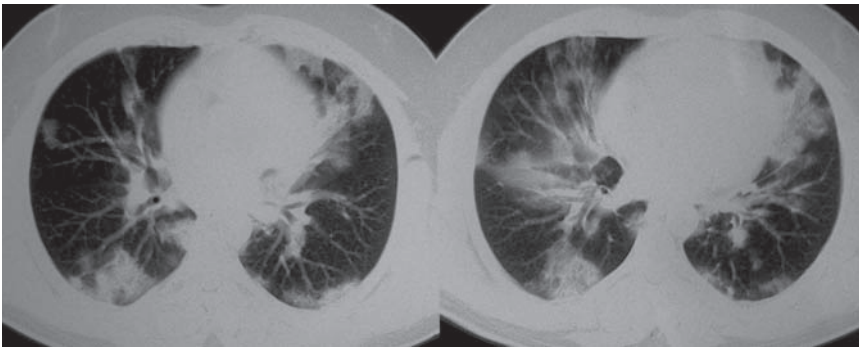


Fig. 1. Axial images from chest computed tomography examination in a patient with swine influenza pneumonia. Images show bilateral patchy infiltration on admission day. The patient was discharged from hospital as cured. Bilateral infiltration was seen more frequently in the patients with S-OIV infection ($n=19$, 57.6%) than negative group ($n=7$, 30.4%) ($p=0.044$)

creatinase levels in swine influenza pneumonia is consistent with previous reports of pneumonia associated with S-OIV in Mexico, most likely due to myositis [4].

In our study, the mortality rate of swine influenza pneumonia (24.2%) was higher than in the negative group (8.7%), but this finding was not statistically significant ($p=0.172$). We do not currently know whether our patients had coinfection with other respiratory viruses. During the 1918 pandemic, a large number of deaths were associated with bacterial infection [23], 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 during hospitalisation. Delayed admission, delayed initiation of oseltamivir therapy and coinfection with other respiratory viruses could be contributing factors for death in our patients. Higher mortality rates and higher frequency of ARDS and MV as well as lower mean PO₂ values in the patients with swine influenza pneumonia show that there was a tendency towards severe illness, as compared with community-acquired pneumonia.

In a study from California, 102 of 227 mechanically ventilated patients with S-OIV infection died [7]. In our study, the small number of mechanically ventilated patients may have skewed the results. In a report from Mexico, most deaths occurred in patients with S-OIV pneumonia who required MV on admission [4]. Another possible cause of high mortality amongst our patients who required MV could be that 8 of 8 patients had transitioned to MV on the first day of admission.

Perez-Padilla et al. [4] reported the clinical and epidemiological features of the first 18 patients with laboratory-confirmed S-OIV in Mexico. All 18 patients had radiologically confirmed pneumonia with bilateral patchy alveolar opacities (predominantly basal), affecting three or four lung quadrants in 11 patients. Bilateral infiltrates were seen in 66% (66/100) of the patients in a report from the United States [3], 94% (64/68) of the patients in a report from China [24] and 59% (10/17) of the patients in a report from Korea [25]. Prachi et al. [26] demonstrated that 71% (20/28) of the patients with S-OIV infection had bilateral

involvement on chest radiograph. In this report, 93% of patients that required ICU admission had extensive disease involving ≥ 3 lung zones and all of them had bilateral opacities. Champunot et al. [13] reported that 79.2% (19/24) of the patients had multilobular or bilateral diffuse infiltrate on chest X-ray. The report from New Zealand showed that 48% of the patients had multi-lobar infiltrates [27]. One of the remarkable findings in our study was that 27% of the patients with swine influenza pneumonia had infiltration extending throughout the lung zone, whereas there was not any infiltration of the entire lung zone in the negative group. Bilateral infiltration (Fig. 1) was seen more frequently in swine influenza pneumonia than in the negative group ($p=0.044$). Based on these findings, widespread infiltrations should alert physicians about distinguishing swine influenza pneumonia from community-acquired pneumonia.

Our study has several limitations. Firstly, most of the patients were adult (only 3 patients were less than 16 years of age). Secondly, the numbers of patients with and without S-OIV infection were too small to acquire strong statistical data.

S-OIV pneumonia is a complication of S-OIV infection and can cause serious illness. Although our radiological or clinical data show significant differences between the patients with S-OIV pneumonia and the negative group, we suggest that no specific constellation seems to be typical of H1N1-associated pneumonia. In conclusion, each patient presenting with signs of pneumonia during pandemic should be tested for Influenza A.

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Conflict of interest

No financial or other potential conflicts of interest exist.

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