The Role of Readily Available Clinical, Laboratory and Radiologic Findings in Distinguishing A/H1N1/2009 Influenza from Other Causes of Acute Febrile Respiratory Illness under Pandemic Conditions

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ABSTRACT: **Background:** During an influenza pandemic, clinicians need easily available clinical and laboratory criteria to distinguish influenza from similar respiratory illnesses. We compared A/H1N1/2009-polymerase chain reaction (PCR)-positive and matched PCR-negative hospitalized patients with suspected H1N1 influenza to identify factors that could assist physicians at patient admission.

Objectives: To identify factors significantly associated with A/H1N1/2009 infection.

Methods: A group of 145 patients with PCR-confirmed A/H1N1 2009 influenza admitted between 27 May 2009 and 3 December 2009 was matched with 145 PCR-negative patients by age, epidemiological week and pregnancy status. Epidemiological and clinical parameters and radiological findings on initial chest X-ray were compared between the two groups.

Results: Asthma (PCR+ 26%, PCR- 12%, $P = 0.006$) and military service (PCR+ 13%, PCR- 4%, $P = 0.15$) were associated with PCR-positive status in non-pregnant patients. At presentation, fever, cough, myalgia and fulfilling the pandemic influenza case definition were significantly more frequent in non-pregnant PCR+ patients (62/90/43/59% in PCR+ versus 38/69/30/35% in PCR-). In pregnant patients, fever and fulfilling the case definition were significantly associated with PCR-positive status. Mean leukocyte and absolute lymphocyte counts were significantly lower in both pregnant and non-pregnant PCR-positive patients. Significantly more PCR-negative non-pregnant patients (43% vs. 22% PCR+, $P = 0.004$) had abnormal chest X-ray (CXR) findings on presentation. In PCR-positive patients, patchy consolidation and interstitial infiltrates were the most common abnormalities.

Conclusions: Under the conditions generated by the A/H1N1/2009 pandemic, radiological findings did not distinguish reliably between influenza and other febrile respiratory illnesses. Asthma, military service, the pandemic case definition (particularly fever, cough and myalgia) and lymphopenia were associated with confirmed H1N1 infection.

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Beginning in March 2009, a novel pandemic influenza A (A/H1N1/2009) virus appeared and rapidly spread worldwide. In Israel, the first cases were identified in April 2009. Initial cases were imported; at first sporadic, and then increasing from June 2009 as the "Taglit-Birthright" program* brought visiting groups of young Americans into contact with their Israeli peers, frequently those in military service. By mid-June a majority of the cases had been locally acquired, and the pandemic virus continued to spread throughout the population, as in other countries [1]. On 26 July 2009, the Israel Ministry of Health issued national guidelines for the presumptive diagnosis and treatment of A/H1N1/2009 influenza [2], based on the World Health Organization [3] and U.S. Centers for Disease Control pandemic influenza guidelines [4]. Patients were diagnosed with "suspected pandemic influenza" if they had fever and at least one of five criteria: cough, rhinorrhea, sore throat, myalgia, and/or dyspnea, or a severe respiratory illness with no other known cause. Hospital referral was recommended for patients with suspected H1N1 influenza if they presented with signs or symptoms of severe illness or with complications of influenza, among them pneumonia. The WHO reports and

*The "Taglit-Birthright" program provides a 10 day trip to Israel for young Jewish adults aged 18-26. (http://www.birthrightisrael.com)

WHO = World Health Organization

ensuing guidelines subsequently emphasized the possibility of sudden deterioration in patients with pandemic influenza, mainly from risk groups, but also including otherwise healthy adults [5], leading to an increase in hospitalizations for observation of cases that could potentially deteriorate.

In the setting of an influenza pandemic, where management and treatment decisions are based on national guidelines, there is a great need for easily available clinical and laboratory criteria to distinguish influenza and its complications from other similar respiratory illnesses. We compared patients hospitalized with suspected H1N1 influenza during the pandemic period who subsequently were found to be polymerase chain reaction-positive for A/H1N1 2009 influenza with matched PCR-negative patients from the same period, in an attempt to identify factors that could assist physicians in distinguishing influenza from similar illnesses under pandemic conditions.

PATIENTS AND METHODS

STUDY POPULATION AND DATA COLLECTION

Epidemiological data for this study were initially collected as part of the Assaf Harofeh Medical Center ongoing surveillance for cases of suspected pandemic influenza. Assaf Harofeh is an 800-bed tertiary-care university-affiliated hospital in central Israel which serves a mainly urban population of approximately 500,000, including a large neighboring military base, as a first-line facility. Patients admitted with suspected pandemic influenza were treated with oseltamivir and placed in isolation with droplet precautions, according to the guidelines issued by the Israel Ministry of Health [2]. All patients during the study period who were tested for H1N1 influenza on admission or during hospitalization were included in the study. This included both the patients who fulfilled the Ministry of Health criteria for the pandemic influenza case definition (fever plus at least one of five influenza-related symptoms or severe respiratory illness) and patients who did not meet these criteria but were tested by hospital staff due to clinical suspicion and therapeutic and/or epidemiological implications of the test result. PCR for influenza A/H1N1 2009 of nasopharyngeal swabs and/or endotracheal aspirate was performed in the nearby national Central Virology Laboratory*. PCR results were generally available within 24–48 hours; oseltamivir was discontinued for PCR-negative cases.

The study population consisted of patients with PCR-confirmed A/H1N1 2009 aged 18 years old or above admitted between 27 May 2009 and 3 December 2009, each matched with a patient who was PCR-negative for A/H1N1 2009. Patients were matched by age (± 5 years) and epidemiological week (± 3 weeks) of the pandemic. As the Israeli public health policy, similarly to that worldwide, evolved over the first few months of the pandemic, we chose to match PCR-positive patients and PCR-negative controls by epidemiological week in order to counteract a potential bias due to changes in testing and hospitalization criteria at different stages of the pandemic. Patients were also stratified by pregnancy status (≤ 2 weeks postpartum were included in the "pregnant" category)*. The study was approved by the Assaf Harofeh Medical Center Institutional Review Board and patients' confidentiality was respected.

Patients were compared by epidemiological background, medical status and coexistent comorbidities. Data were retrieved from the patients' charts and from the laboratory records. Temperature ≥ 38°C was considered fever, and blood oxygen saturation of ≥ 95% on room air was considered normal. Outcome categories included admission to the intensive care unit and death during hospitalization.

Patients were excluded from evaluation if on review the suspicion of H1N1 influenza appeared to have been raised inappropriately (clinical presentation inconsistent with influenza-like illness, and without the recommendation of an infectious diseases consultant), or if on review H1N1-PCR results were inconclusive.

CHEST X-RAY REVIEW

Chest X-rays were reviewed by a single senior radiologist (G.G.) unaware of the patients' PCR results or discharge diagnosis. Comparison to archived imaging was allowed when available. The chest X-ray on the day of first presentation with suspected influenza A/H1N1 infection (or the following day if not performed on presentation) was included in data analysis. Abnormal films were characterized according to the nature of the pathological findings: unilateral vs. bilateral, interstitial pattern vs. patchy consolidation vs. lobar/segmental consolidation. The presence of pleural effusion and expiratory films were also noted. Patients were excluded from chest X-ray analysis (while being included in evaluation for all other parameters) if no presentation chest X-ray was available, if technical quality precluded evaluation, or if underlying lung pathology precluded interpretation.

STATISTICAL ANALYSIS

Categorical variables were compared using the chi-square or Fisher exact test as appropriate. Continuous variables were compared using the Kruskal-Wallis test. Parameters that were significantly associated with PCR positivity ($P < 0.1$) were entered into a multivariate regression model. Multivariate

*Central Virology Laboratory, Israel Ministry of Health, Sheba Medical Center, Tel Hashomer, Israel

PCR = polymerase chain reaction

* As per CDC recommendations during the pandemic, which included the two first weeks postpartum in the period of pregnancy-associated risk factors for severe influenza (Pandemic H1N1 2009 guidelines; replaced by current influenza guidelines in MMWR of January 21, 2011 / 60(RR01);1-24, which retain the same approach to the immediate postpartum period).

logistic regression analysis was used to assess the association between patient characteristics and positive PCR results for A/H1N1/2009 or unfavorable outcome. A P value ≤ 0.05 was considered statistically significant. SPSS version 18 (SPSS Inc. Chicago, Il, USA 2008) was used for the analyses.

RESULTS

A total of 295 patients hospitalized between 11 May 2009 and 3 December 2009 with suspected A/H1N1/2009 influenza were enrolled in the study. Five patients were excluded. Of the remaining 290 patients, 145 were positive by nasopharyngeal PCR for influenza A/H1N1/2009 and 145 were PCR-negative. Chest radiography was performed on 280 patients (97%) at or soon after presentation. Twenty-six were excluded from CXR analysis (7 due to underlying pulmonary pathology, 13 to expiratory films and 6 to poor technical quality), giving a total of 254/290 patients (88%, 130 PCR+, 124 PCR-) with an evaluable CXR: 181/210 (86%, 94 PCR+, 87 PCR-) of non-pregnant patients and 73/80 (91%, 36 PCR+, 37 PCR-) of pregnant patients had an evaluable CXR; 148/328 (58%) included a lateral film.

Patient epidemiological characteristics, symptoms and laboratory results are summarized in Table 1 (univariate analysis), with multivariate analysis in Table 2. Asthma (26%) was the most common factor associated with PCR-positive status in non-pregnant patients; active smoking (32%) was the most common associated factor in PCR-negative non-pregnant patients. Military service was also found to be significantly associated with PCR-positive status (PCR+ 13%, PCR- 4%, $P = 0.015$) in non-pregnant patients. Patients with confirmed H1N1 influenza were more likely than those who were PCR negative to be febrile (62% non-pregnant, 51% pregnant), to fulfill the influenza case definition and to have lower white blood cell and lymphocyte count. Myalgia and cough were also more frequent in PCR-positive than PCR-negative non-pregnant patients.

Radiological findings on presentation are summarized in Table 3. In non-pregnant patients, abnormal findings on chest X-ray were more common in PCR-negative patients; unilateral pathology (26%) and patchy consolidation (24%) were the most common findings.

Five PCR-positive patients had an adverse outcome (ICU admission or death). No epidemiological or clinical parameters were found independently correlated with unfavorable outcome when entered into a multivariate regression model. All five patients had bilateral pathology on presentation CXR.

Table 1. Clinical and laboratory characteristics of patients PCR positive for A/H1Ni/2009 influenza compared with PCR-negative patients

	Non-pregnant			Pregnant		
	H1N1 PCR+	H1N1 PCR-	*P* value	H1N1 PCR+	H1N1 PCR-	*P* value
	No. (%)	No. (%)		No. (%)	No. (%)	
	N=106	N=104		N=39	N=41	
Male	**49 (46.2)**	**47 (45.2)**	**0.880**			
Age (mean) ± SD	39.6 ±16	41.8 ±17	0.339	27.6 ± 4.5	29.7 ± 6.1	0.177
Underlying conditions						
IDF	14 (13.2)	4 (3.8)	0.015	2 (5.1)	0 (0)	0.234
Active smoking	16 (15.1)	33 (31.7)	0.004	0	0	
Immunosuppression	11 (10.4)	14 (13.5)	0.490	0	0	
COPD	7 (6.6)	12 (11.5)	0.213	0	0	
Asthma	28 (26.4)	12 (11.5)	0.006	2 (5.1)	5 (12.2)	0.433
Diabetes	14 (13.2)	21 (20.2)	0.174	0	3 (7.3)	0.241
Neurologic disease	10 (9.4)	9 (8.7)	0.844	0	0	
Renal insufficiency	5 (4.7)	4 (3.8)	1.000	0	0	
CHF	3 (2.8)	1 (1.0)	0.621	0	0	
Symptoms						
Fever ≥ 38ºC at admission	64 (61.5)	38 (38.4)	0.001	20 (51.3)	11 (26.8)	0.025
Throat pain	38 (35.8)	30 (28.8)	0.278	16 (41.0)	11 (26.8)	0.180
Cough	95 (89.6)	72 (69.2)	<0.001	29 (74.4)	24 (58.5)	0.135
Rhinorrhea	35 (33.0)	23 (22.1)	0.077	12 (30.8)	9 (22.0)	0.370
Myalgia	46 (43.4)	29 (27.9)	0.019	8 (20.5)	4 (9.8)	0.220
Dyspnea	44 (41.5)	40 (38.5)	0.652	9 (23.1)	12 (29.3)	0.529
Case definition	61 (58.7)	35 (35.4)	0.001	17 (43.6)	7 (17.1)	0.010
Chills	17 (16.0)	17 (16.3)	0.952	4 (10.3)	1 (2.4)	0.195
Headache	34 (32.1)	27 (26.0)	0.329			
Diarrhea	8 (7.5)	11 (10.6)	0.444	4 (10.3)	5 (12.2)	1.000
O_2 saturation ≤ 95	20 (20.2)	25 (27.5)	0.239	0 (0)	2 (5.6)	0.494
Laboratory values ± SD						
WBC (mean) x10^3/ml	6.88 ± 3.0	9.49 ± 4.7	<0.001	8.70 ± 2.8	10.84 ± 3	0.003
ALC (mean) x10^3/ml	1.11 ± 0.7	1.34 ± 0.7	0.008	1.01 ± 0.46	1.45 ± 0.6	0.001
PLT (mean) x10^3/ml	197.4 ± 71	216.1 ± 87	0.043	200.9 ± 60	218.4 ± 59	0.118
Sodium (mean) mmol/L	137.0 ± 4	136.4 ± 13	0.263	135.0 ± 3	136.3 ± 3	0.034
CK (mean) U/L	152.6 ± 171	250.5 ± 1254	0.013	208.7 ± 350	69.9 ± 72	0.225
LDH (mean) U/L	388.8 ± 149	400.3 ± 287	0.929	354.6 ± 95	314.2 ± 67	0.009

Parameters that were available for less than 100% of patients (PCR-/PCR+):
Non-pregnant: O_2 saturation available for 91/99, temperature 99/104, case definition (calculated) 99/104, sodium 103/106, CK 95/90, LDH 93/99
Pregnant: O_2 saturation 36/33, PLT 40/39, sodium 41/37, CK 7/7, LDH 39/37
SD = standard deviation, IDF = Israel Defense Forces (military service), COPD = chronic obstructive pulmonary disease, CHF = congestive heart failure, WBC = white blood cell count, ALC = absolute lymphocyte count, PLT = platelet count, CK = creatinine kinase, LDH = lactate dehydrogenase, O_2 = oxygen

DISCUSSION

In the present study, we compared 145 H1N1-PCR-positive patients with 145 matched PCR-negative patients among those with suspected pandemic influenza. As it became clear in the first months of the pandemic that young adults were disproportionately affected by H1N1/2009 influenza [5], we elected to match patients by age in order to look for

CXR = chest X-ray
ICU = intensive care unit

parameters that could assist in the diagnosis of influenza in the situation of an ongoing pandemic.

In non-pregnant patients we found asthma and current military service to be the major epidemiological factors associated with positive status, while active smoking was associated with negative status. With respect to presenting symptoms, fulfilling the "case definition" criteria of fever plus at least one of five influenza-related symptoms was also significantly associated with positive status.

Other studies have found asthma to be a frequent comorbidity in patients presenting with H1N1-related illness. In a British study [6] asthma was the most frequent comorbidity in patients hospitalized with H1N1 influenza and was present in 124 of 405 admitted adults (31%); asthma was also reported in 39.5% of 43 H1N1-related admissions in New York early in the pandemic [7]. In studies of severe illness, asthma was less frequent as other comorbidities played a more significant role [8].

A recent UK study [9] comparing patients admitted with H1N1 influenza-related pneumonia during the recent pandemic to a cohort admitted with community-acquired pneumonia also found asthma to be associated with H1N1. Although they found chronic obstructive pulmonary disease and heart failure to be associated with non-H1N1 community-acquired pneumonia, this is probably due to a difference in methodology from our study. The non-matched UK study found age ≥ 65 to be associated with non-pandemic community-acquired pneumonia; it is thus not surprising that they also found an increased incidence of comorbidities in the CAP group. In addition, the UK group compared cohorts from different locations and time periods: a national H1N1 cohort during the pandemic was compared with a local CAP cohort excluding the pandemic period, whereas we compared matched groups of patients admitted under the same conditions during the pandemic period. Another non-matched comparative study, of patients hospitalized with CAP during the pandemic in southern Israel [10], found a higher incidence of chronic lung disease in the non-H1N1 group. This group was also significantly older, and no distinction was made between asthma and other pulmonary disease. In addition, patients were significantly more frequently female, of Bedouin Arab (as compared to predominantly Jewish) origin, and of lower socioeconomic status than controls, which is likely to have affected the frequency of chronic illness in the study groups.

Military service was also found to be significantly associated with H1N1 positivity, probably due to particular local circumstances. In June, a major increase in cases was noted among American participants in the "Taglit-Birthright" project and their Israeli contacts, with the subsequent development of sustained local transmission [1]. Many of the contacts were Israel Defense Forces soldiers assigned to accompany the Taglit groups. The circumstances of military service, with a large number of young adults living in relatively close quarters, facilitate the spread of respiratory infections [11]. As IDF soldiers also frequently return to their families and friends on weekends, this presumably contributed to community transmission. While the Israeli combination of military service with exposure to a visiting population would seem to be unique, several other countries have reported outbreaks of H1N1 influenza in military facilities [12,13].

The absence of association between any particular risk factor and PCR-positive status among pregnant patients can be explained by the fact that pregnancy itself is a known risk factor for severe and complicated influenza, and was reported to be associated with an increased incidence of H1N1 influenza complications in the first months of the pandemic [14].

Among presenting symptoms, both fever alone and the "case definition" criteria of fever plus at least one of five influenza-related symptoms were associated with PCR-positive status, in both pregnant and non-pregnant patients. The alternative case definition criteria of "severe respiratory illness with no other known cause" was not included in data analysis due to the difficulty both in defining "severe" illness and in excluding other causes in cases where an identified pathogen could represent superinfection (i.e., influenza and secondary bacterial pneumonia). Among influenza-related symptoms, we found cough and myalgia to be significantly more frequent in PCR-positive non-pregnant patients than in PCR-negative. This is similar to the results of a comparative Israeli emergency room study [15], where fever, cough and myalgia were the only influenza-related symptoms significantly associated with H1N1 influenza, and to the study by Saidel-Odes et al. [10]. The fact that a relatively low percentage of patients met the clinical case definition for H1N1 influenza is due to the fact that our study included all hospitalized patients tested for pandemic influenza during the study period. Whereas the Ministry of Health guidelines required fever or severe illness, hospital testing policy was broadened to include patients who did not meet the case definition (mainly due to absence of fever) where the result was likely to influence case or infection control management: immune-compromised or debilitated patients with respiratory illness who might not be able to mount a febrile inflammatory response to infection, and pregnant or parturient women with upper respiratory symptoms due to the potential risk of exposure to other women in the department. The inclusion of these patients in the study, while to some extent limiting the ability to draw conclusions about patients meeting the Health Ministry criteria, provides interesting information on hospitalized patients with PCR-positive pandemic influenza who would not have been identified using the Ministry's case definition. It is noteworthy that despite the significant association of fever and case definition

CAP = community-acquired pneumonia

IDF = Israel Defense Forces

criteria with PCR-positive status, 38% of positive cases were afebrile and 41% failed to fulfill the case definition. While this does not necessarily indicate that these cases required treatment, our results could potentially have implications both for infection control policy and clinical care.

Overall, our results, together with the above-mentioned studies of H1N1/2009 presenting symptoms, tend to validate the case definition used during the pandemic. However, these results also point to fever, myalgia and cough as potentially valuable for distinguishing H1N1 influenza from other respiratory illnesses presenting in the situation of an ongoing influenza pandemic. Similarly, Cunha and co-authors [16] developed a rapid scoring system in which fever and severe myalgias were the two symptoms considered to be most predictive of H1N1 influenza as compared to other community-acquired respiratory infections.

Among the laboratory tests commonly available in the emergency room, mean white blood cell count, mean absolute lymphocyte count and mean absolute neutrophil count were all significantly lower in both pregnant and non-pregnant patients with H1N1. The percentage of PCR-positive patients with absolute lymphocyte count < 1000 was also significantly lower than for PCR-negative. This is consistent with observations by Cunha and others [16,17] as well as with those of the comparative study by Bewick et al. [9], although not with the results of Shlomai and collaborators [15]. The latter group, however, compared only minimum lymphocyte count between H1N1-negative and positive groups, finding no significant difference. This may also be due in at least in part to a selection bias: lymphopenia was one of the factors that encouraged a clinical diagnosis of influenza during the pandemic. Given that a similar bias is likely to exist in our study, the association we found between lymphopenia and positive status is all the more significant.

The results of CXR analysis in our study also contribute to the understanding of initial assessment for H1N1 influenza under pandemic conditions. In non-pregnant patients, we found the presence of any radiological abnormalities on presentation to be associated with H1N1-negative status. Unilateral pathology and patchy consolidation were also significantly associated with negative status. The latter finding was unexpected, since from the earliest days of radiology primary influenza pneumonia was typically observed to be associated with patchy or interstitial infiltrates [18]; this appears to also be true of the A/H1N1/2009 strain. A number of recent studies of patients hospitalized with PCR-confirmed H1N1 influenza also found patchy infiltrates to be the most frequent pathological finding on chest X-ray [19,20]. The most likely explanation of our findings is related to the influenza pandemic itself, and to the effect of national pandemic guidelines. According to these guidelines, influenza-associated

Table 2. Multivariate analysis of variables associated with A/H1N1/2009 PCR-positive status

	Non-pregnant		Pregnant	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
IDF service	4.3 (1.1–17.8)	0.042		
Fever ≥ 38ºC on admission	2.3 (1.1–5.1)	0.036		
Cough	4.2 (1.5–11.6)	0.007		
WBC (mean) x10^3/ml	0.9 (0.8–1.0)	0.026	0.7 (0.6–0.9)	0.012
ALC (mean) x10^3/ml			0.2 (0.0–0.6)	0.006

IDF = military service (Israel Defense Forces), WBC = white blood cell count, ALC = absolute lymphocyte count

Table 3. Radiologic findings of PCR-positive and PCR-negative patients hospitalized with suspected A/H1N1/2009 influenza

	Non-pregnant			Pregnant		
CXR findings	H1N1 PCR+ No. (%)	H1N1 PCR- No. (%)	*P* value	H1N1 PCR+ No. (%)	H1N1 PCR- No. (%)	*P* value
Patients with evaluable admission CXR	94 (100)	87 (100)		36 (100)	37 (100)	
Any CXR abnormality	21 (22.3)	37 (42.5)	0.004	12 (33.3)	10 (27.0)	0.557
Unilateral pathology	11 (11.7)	23 (26.4)	0.011	6 (16.7)	3 (8.1)	0.308
Bilateral pathology	10 (10.6)	14 (16.1)	0.280	6 (16.7)	7 (18.9)	0.801
Interstitial pathology	10 (10.5)	12 (13.8)	0.499	3 (8.3)	3 (8.1)	1.000
Patchy consolidation	10 (10.6)	21 (24.1)	0.016	8 (22.2)	7 (18.9)	0.727
Lobar/segmental consolidation	3 (3.2)	5 (5.7)	0.484	0	0	NA

NA = not available

Table 4. Characteristics of severe (ICU admission or fatal) cases among all A/H1N1/2009 PCR-positive patients

	Non-ICU admission/fatal cases (n=140) No. (%)	ICU admission (n=4) or fatal cases (n=1) No. (%)	*P* value
Mean symptom duration (days) ± SD	2.9 ± 2	5.0 ± 2	0.032
Mean lymphocyte count (x 10^3/ml) ± SD	1.09 ± 0.7	1.00 ± 0.5	0.089
Mean sodium mmol/L ± SD	136.6±4	132.4±3	0.010
Radiological findings			
Any CXR abnormality	28 (22.4)	5 (100.0)	0.001
Bilateral pathology	11 (8.8)	5 (100.0)	< 0.001
Interstitial pathology	10 (7.9)	3 (60)	0.007
Patchy consolidation	16 (12.8)	2 (40)	0.141
Lobar/segmental consolidation	3 (2.4)	0	1.000
Pleural effusion	4 (3.2)	0	1.000

Patients included in CXR analysis (non-severe/severe): 125/5
CXR = chest X-ray

pneumonia was considered to be "severe influenza" and was frequently interpreted as requiring hospitalization due to the possibility of rapid clinical deterioration [2]. Fever and a positive chest X-ray were considered to meet the criteria for suspected H1N1, even in the absence of other influenza-associated symptoms. The pandemic situation thus increased the number of patients hospitalized not only with influenza-related illness but also with non-influenza CAP. As influenza-related illness also included non-pneumonia complications of influenza, this favored a higher percentage of radiological abnormalities in the non-H1N1 group. This is in clear contrast to the comparative study by Bewick et al. [9], which included only patients with radiographic findings compatible with pneumonia and compared a H1N1 cohort to a non-pandemic CAP cohort, finding bilateral consolidation to be associated with H1N1-related pneumonia. Our results indicate that, under pandemic conditions, classic influenza-associated radiographic findings such as bilateral pathology or patchy consolidation are not indicative of pandemic influenza as compared to other etiologies of community-acquired pneumonia.

Among PCR-positive patients, the five who were eventually admitted to the intensive care unit (four patients) or died (one patient) had a significantly longer mean duration of symptoms before hospitalization than non-ICU/fatal cases [Table 4]. This association between delay of oseltamivir therapy and adverse outcome was noted early in the pandemic [21] and was a factor in shaping the guidelines mandating early treatment. Mean lymphocyte count was lower in the ICU/fatal cases, although not significantly, perhaps due to the small number of severe cases.

All five ICU/fatal cases had bilateral findings on initial CXR, with interstitial infiltrates in 3 cases (60%) and patchy infiltrates in 2 cases (40%). This is similar to the studies of Aviram and colleagues [19] and others [20], who found bilateral and multiple lung zone involvement to be significantly associated with adverse outcome. Shaham and team [22], when comparing imaging (CXR and computed tomography) results of survivors versus non-survivors in H1N1-positive ICU patients, found no significant difference in radiological findings. Given that all study patients were admitted to the ICU, with high overall mortality (45%), abnormal radiological findings in all patients, and the fact that mortality was associated with increased age and preexisting illnesses, the results could simply indicate that all included patients had severe H1N1 illness, with survival depending more on background factors. Although it is difficult to draw definitive conclusions from a small number of severe cases, our findings concur with a number of previous studies to indicate that patients with bilateral infiltrates on initial chest X-ray should be closely followed for signs or symptoms of clinical deterioration.

STUDY LIMITATIONS

The major limitation of this study is that it is retrospective and based primarily on information available from review of the patients' electronic record. It is possible that relevant epidemiologic and clinical factors would have been present in additional patients in a prospective study format. Specifically, body mass index, which was found by others [8] to be associated with severe H1N1 influenza, was not available for most patients and thus could not be evaluated in this study. In addition, since the study included patients over different periods of the pandemic, there were ongoing changes in testing and hospitalization criteria. However (see Methods), the matching was also done by epidemiological week in order to minimize bias introduced by the pandemic and response evolution. As mentioned above, the decision to include all tested hospitalized patients, rather than only those meeting the case definition, limits to some extent the applicability of our conclusions; however, this also provides information as to the epidemiology and clinical characteristics of hospitalized patients with influenza not meeting the Health Ministry criteria.

CONCLUSIONS

During an influenza pandemic, chest radiology cannot reliably distinguish between influenza and other infectious causes of acute respiratory illness. The very nature of pandemic guidelines affects the criteria for presumptive diagnosis and hospitalization, and thus even radiological findings traditionally associated with influenza are frequent in non-influenza patients. Asthma, however, remains a risk factor significantly associated with influenza infection in admitted patients. The case definition criteria of fever plus at least one of five symptoms, particularly cough and myalgia, remain suggestive of influenza as the cause of acute respiratory illness, as does lymphopenia. Bilateral infiltrates in a patient with suspected influenza should prompt close monitoring for eventual clinical deterioration.

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Capsule

Taming microglia for treating multiple sclerosis

Multiple sclerosis (MS) is a severely debilitating degenerative disease of the central nervous system. Resident macrophages of the brain, called microglia, are thought to be an important driver of disease. Factors that promote the conversion of pro-inflammatory, or "M1" microglia, which are thought to be the type of microglia that contribute to disease, into less dangerous, immunoregulatory "M2"-type microglia, are of therapeutic interest. Starossom et al. identified one such factor, the endogenous glycan-binding protein Galectin-1 (Gal1). In a mouse model of MS, Gal1 was expressed during the acute and chronic stages of disease by astrocytes and some populations of immune cells. Gal1 bound preferentially to M1 microglia in a glycan-dependent manner, and once bound, it inhibited the pro-inflammatory phenotype of M1 microglia by retaining the phosphatase CD45 on the cell surface. This resulted in the dephosphorylation, and therefore downmodulation, of several downstream pro-inflammatory signaling molecules. The effects of Gal1 on M1 microglia were primarily the result of astrocyte-produced Gal1. Finally, the authors showed that mice deficient in Gal1 experienced enhanced axonal damage, whereas treatment of mice with Gal1-treated microglia or with Gal1 itself had a therapeutic effect, which suggests that Gal1 may be a potential therapeutic target in MS.

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Two things fill my mind with ever-increasing wonder and awe, the more often and the more intensely the mind of thought is drawn to them: the starry heavens above me and the moral law within me

Immanuel Kant (1724-184), German philosopher