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PAPER

PATHOLOGY/BIOLOGY

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2009 H1N1 Fatalities: The New Mexico Experience

ABSTRACT: Histopathologic features of New Mexico 2009 H1N1 fatalities have not been representative of those reported nationwide. We retrospectively reviewed medical records of all New Mexico 2009 pandemic influenza A (pH1N1) fatalities (n = 50). In cases in which autopsy was performed (n = 12), histologic sections and culture results were examined. In contrast to previously published studies, the majority of our fatalities did not have diffuse alveolar damage (DAD) (2/12; 16.7%). Common findings included pulmonary interstitial inflammation and edema, tracheobronchitis, and pneumonia. Two cases had significant extra-pulmonary manifestations: myocarditis and cerebral edema with herniation. The majority had a rapid disease course: range from 1 to 12 days (median, 2 days), and Native Americans were disproportionately represented among fatalities. These findings suggest that New Mexico H1N1 fatalities generally did not survive long enough to develop the classic picture of DAD. Pathologists should be aware that H1N1 may cause extra-pulmonary pathology and perform postmortem cultures and histologic sampling accordingly.

KEYWORDS: forensic science, autopsy, pulmonary pathology, Type A Influenza, H1N1 virus, 2009 pandemic

In March of 2009, the first cases of infection by 2009 pandemic influenza A (pH1N1) virus were reported from Mexico. The virus rapidly spread to the United States and Canada, and subsequently worldwide, causing the first influenza pandemic since 1968 (1,2). As of March 2010, more than 213 countries or territories had reported laboratory-confirmed cases of pH1N1 influenza, which resulted in over 17,483 pH1N1 deaths (3). This figure undoubtedly represents a significant underestimate of the actual fatality rate, as many decedents never sought medical attention and those who did were often not referred for influenza testing. The Centers for Disease Control (CDC) estimates that there were over 12,400 pH1N1-related deaths occurring from April 2009 to April 2010 in the United States alone (4).

There have been three previous influenza pandemics: 1918 (H1N1), 1957 (H2N2), and 1968 (H3N2). All viruses arose either wholly or partially from nonhuman reservoirs (5). pH1N1 influenza is a novel combination of viral genes that appear most closely related to swine-lineage influenza (3,5). As compared to seasonal H1N1 influenza, pH1N1 influenza has been shown to result in markedly weaker activation of the human innate immunity response, which may help explain the virulence of this virus (6). In autopsy studies of fatal seasonal influenza cases, immunohistochemical as well as *in situ* hybridization studies have shown the viral antigens to be primarily located within the upper respiratory tract, that is, tracheal, bronchial, and large bronchiolar epithelial cells (7,8). This is in contrast to pandemic influenza fatalities, in which antigens may be noted within the upper respiratory tract, but are predominantly located in the lower respiratory tract within pneumocytes and alveolar macrophages (9,10).

There have been a limited number of studies addressing the histopathologic features of pH1N1 influenza fatalities (9,11–15). As with other forms of influenza, histologic manifestations are not specific. For instance, viral cytopathic changes are not evident by light microscopy. Additionally, secondary bacterial pneumonia can occur, compounding the difficulty of identifying primary viral disease (7). Most early studies agreed, however, that diffuse alveolar damage (DAD) was one of the most reliable and significant features of pH1N1 fatalities. The first New Mexican pH1N1 death occurred in August of 2009, when a 45-year-old woman with end-stage liver disease expired (16). The New Mexico Department of Health subsequently reported 49 additional pH1N1 deaths in 2009. It quickly became evident that the features seen in New Mexican pH1N1-autopsied fatalities were not typical of those being reported nationwide. New Mexico is an ethnically and racially diverse state with a large Native American population, among others. We hypothesized that this population diversity might predict a similar diversity of clinicopathologic findings in 2009 New Mexico pH1N1 fatalities.

Materials and Methods

Nonautopsied H1N1 Fatalities

We collaborated with the New Mexico Department of Health to retrospectively review medical records and investigative findings of all nonautopsied pH1N1 fatalities reported in New Mexico in 2009. Patient's clinical and epidemiologic features examined included age, gender, race, symptoms, means of diagnosis, medical interventions, and comorbidities.

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Autopsied H1N1 Fatalities

We conducted a search of the New Mexico Office of the Medical Investigator computer database to identify all pH1N1-positive fatalities autopsied in 2009. A retrospective examination of autopsy reports, medical records, and scene investigative findings was performed. Cases in which pH1N1 infection at death was incidental rather than causative were excluded from further study. All available microscopic slide sections were independently reviewed by a pathologist. All respiratory sections were additionally reviewed by a pathologist with pulmonary pathology expertise. Except in cases of an autopsy with family-imposed restrictions, standard procedure was to take sections of heart, lungs, liver, kidneys, and brain, at minimum. Respiratory sections were assessed for seven histologic features: tracheitis, bronchitis/bronchiolitis, intra-alveolar edema, intra-alveolar hemorrhage, interstitial inflammation, pneumonia, and hyaline/fibrinous membranes (i.e., DAD).

Postmortem viral and bacterial studies in autopsied cases were performed by the New Mexico Scientific Laboratory Department. Viral samples for influenza real-time reverse transcription polymerase chain reaction (rtRT-PCR) underwent nucleic acid extraction using one of three kits: the Qiagen QIAamp Viral RNA Mini Kit (Qiagen, Valencia, CA), a Roche MagNA Pure Compact Nucleic Acid Isolation Kit, or a Roche MagNA Pure Compact RNA Isolation Kit (Roche Diagnostics, Indianapolis, IN). Extracts were then tested using the CDC Human Influenza Virus rtRT-PCR Detection and Characterization Panel, which universally detects Type A Influenza viruses, and specifically detects all swine A influenza viruses and Swine H1 influenza (17). Select cases were additionally sent to the CDC in consultation.

Results

General Patient Characteristics

There were 53 pH1N1-positive fatalities occurring in 2009 reported to the New Mexico Department of Health. In three of these cases, autopsy revealed that pH1N1 was incidental rather than instrumental in causing the death: in one instance a patient expired of a ruptured myocardial infarction, and in the other two of a mixed drug intoxication. These three cases were thus excluded from further study. In the remaining 50 cases, the diagnosis of pH1N1 influenza was generally made via RT-PCR (43/50; 86%) or direct immunofluorescence assay (5/50; 10%) (Table 1). In three cases, the patient tested positive for Type A Influenza by means of rapid influenza diagnostic testing. As essentially the only subtype of Type A Influenza circulating in New Mexico at this time was pH1N1, these cases met New Mexico Department of Health criteria for inclusion as pH1N1 deaths.

The men to women ratio was 29:21. The age range was broad, spanning 2 months–89 years (mean, 44.2 years), with the largest decade peaks occurring in the 41–50 and 51–60 year spans. Race/ethnicity, in order of decreasing frequency, was as follows: Hispanic, Caucasian, and Native American. The most common adult comorbidities were hypertension, diabetes, and chronic obstructive pulmonary disease/emphysema, while the most common youth comorbidities were asthma and malignancy. Non-Native American adults had a higher prevalence of comorbidities than did Native American adults, and in most cases comorbidities were multiple: 87.5% versus 75%. A larger percentage of youths were obese/morbidly obese than were adults: 40% versus 20%. As compared to other races, a greater percentage of Native American fatalities were obese: 36.4% (4/11) versus 20.5% (8/39). The most common presenting symptoms overall were cough, dyspnea, fever, myalgia, and nausea/vomiting. More than half of patients received antiviral treatment (generally Oseltamivir) and were mechanically ventilated prior to death.

TABLE 1—*Characteristics of 2009 H1N1 fatalities in New Mexico.*

Characteristics	Number
Male gender	29/50 (58%)
Age range (median)	2 months–89 years (44.2 years)
0–10 years	5/50 (10%)
11–20 years	5/50 (10%)
21–30 years	5/50 (10%)
31–40 years	2/50 (4%)
41–50 years	9/50 (18%)
51–60 years	13/50 (26%)
61–70 years	6/50 (12%)
71–80 years	3/50 (6%)
81–90 years	2/50 (4%)
Race	
Hispanic	21/50 (42%)
Caucasian	18/50 (36%)
Native American	11/50 (22%)
Comorbidities of adults* (n = 40)	
COPD/emphysema	11/40 (27.5%)
Asthma	6/40 (15%)
Diabetes mellitus	13/40 (32.5%)
Hypertension	15/40 (37.5%)
Coronary artery disease	6/40 (15%)
Congestive heart failure	6/40 (15%)
Cirrhosis	7/40 (17.5%)
Malignancy	5/40 (12.5%)
Obesity (BMI ≥ 30)	8/40 (20%)
Comorbidities of youths† (n = 10)	
Asthma	3/10 (30%)
Obesity	4/10 (40%)
Malignancy	1/10 (10%)
Clinical symptoms	
Cough	28/50 (56%)
Dyspnea	26/50 (52%)
Pharyngitis	6/50 (12%)
Nausea/vomiting	11/50 (22%)
Diarrhea	6/50 (12%)
Fever (temperature >38°C or 100.4°F)	14/50 (28%)
Myalgia	13/50 (26%)
Altered mental status	9/50 (18%)
Headache	6/50 (12%)
Rhinorrhea	2/50 (4%)
Medical interventions	
Antiviral treatment	27/50 (54%)
Mechanical ventilation	29/50 (58%)
Laboratory diagnosis	
Real-time polymerase chain reaction–positive	43/50 (86%)
Direct immunofluorescence assay–positive	5/50 (10%)
Rapid influenza test–positive	2/50 (4%)

*Adult = patient >18 years of age.
†Youth = patient <18 years of age.
COPD, chronic obstructive pulmonary disease; BMI, body mass index.

Autopsied Cases: Viral Studies

In three cases, the diagnosis of pH1N1 was made antemortem: in one case, a rapid nasopharyngeal swab was positive for Type A Influenza and in two other cases, the diagnosis was made on the basis of rtRT-PCR. Both viral cultures in these same two cases were negative, which would be consistent with the increased sensitivity of PCR. Postmortem PCR and viral cultures were

performed on nasopharyngeal swabs in 11/12 cases: PCR was positive in 10, and cultures positive in nine. Concurrent lung viral cultures were performed in 9/12 cases, and at least one lung was positive in five cases, while both lungs were negative in four cases. As our PCR protocol is not yet validated for lung swabs, PCR was only performed on cases in which lung viral cultures demonstrated growth, and isolates could be used for PCR. The one case which did not have postmortem PCR performed and the one which had negative postmortem PCR were both positive by antemortem tests.

Autopsied Cases: Bacterial Studies

In 9/12 cases, postmortem lung bacterial cultures were performed. Four of these samples showed no growth. One showed growth with no microscopic evidence of pneumonia and so was considered consistent with postmortem contamination. Of the four cases that grew organisms, one had microscopic evidence of pneumonia, two were deemed postmortem contamination (one was rare organisms only and mixed, while the other was not a common etiologic agent of pneumonia, i.e., diptheroids). Two were deemed true positives: one was *group A Streptococcus* and the other was *Streptococcus pneumoniae*. Of the three cases which had no postmortem lung cultures, one had an antemortem tracheal culture that showed no growth, one had an antemortem sputum culture that was positive for *Staphylococcus aureus*, and one had no antemortem or postmortem bacterial cultures performed.

Autopsied Cases: Clinical and Macroscopic Features

There were 12 autopsied pH1N1 fatalities in New Mexico in 2009 (Table 2). Five of the fatalities were children aged 6 or under, one was a 17-year-old, and the remainder were adults. The majority of fatalities had a relatively rapid disease course: the range from symptom onset to death was 1–12 days (median, 2 days). In one case, the decedent was a transient, and the time of symptom onset was unknown. Anecdotally, in three cases, the family reported a distinct period of several hours in which there was apparent remission/improvement of symptoms, before a sudden decline and death.

Overall, the adult lungs were heavier than normal: the average weight of a right lung was 815.7 g (vs. expected 450 g) while the average weight of a left lung was 617.1 g (vs. expected 375 g) (18). Similar trends were seen with the spleen (average weight, 227.1 g). In a few cases, there was grossly purulent mucoid material within upper and lower airways. The majority of the children (4/5) also had lungs and spleens heavier than those of normal infants/children. One infant had weights that were within normal limits. However, this was an infant who was also at the 10th percentile for weight, so these weights may have actually been larger than physiologic norms for him.

TABLE 2—*Histopathologic features of autopsied 2009 H1N1 fatalities in New Mexico.*

Case	Age/Sex	Race	Comorbid	Illness Length	Lung/Spleen Weights (g)	Histologic Features
1	2 months/M	C	——	12 days	RL: 44.6 LL: 38 S: 15	Chronic tracheitis, acute and chronic interstitial inflammation, acute pneumonia
2	6 months/F	C	——	2 days	RL: 96.7 LL: 83.5 S: 32	Chronic tracheobronchitis and interstitial inflammation, alveolar edema
3	4 years/M	NA	——	2 days	RL: 320 LL: 250 S: 83	Chronic tracheobronchitis and interstitial inflammation, alveolar edema, acute pneumonia
4	5 years/F	H	——	1 day	RL: 360 LL: 340 S: 110	Chronic tracheobronchitis and interstitial inflammation
5	6 years/F	NA	Asthma	1 day	RL: 201.1 LL: 164.5 S: 94.4	Chronic bronchitis, acute and chronic interstitial inflammation, alveolar edema and focal hemorrhage, acute focal pneumonia, myocarditis
6	17 years/F	H	——	2 days	RL: 590 LL: 450 S: 250	Chronic tracheobronchitis and interstitial inflammation, alveolar edema, ischemic cerebral changes, medullary intraparenchymal hemorrhage
7	18 years/M	C	Obesity	7 days	RL: 1650 LL: 1500 S: ——	Acute and chronic bronchitis and interstitial inflammation, alveolar edema and hemorrhage, organizing pneumonia with fibrin/hyaline membranes
8	51 years/M	H	COPD, CAD, HTN	1 day	RL: 600 LL: 420 S: 180	Acute and chronic bronchitis w/square meter and interstitial inflammation, alveolar edema, acute pneumonia
9	51 years/F	C	HTN, CHF	2 days	RL: 400 LL: 350 S: 200	Acute and chronic bronchitis w/square meter and interstitial inflammation, chronic tracheitis, acute pneumonia
10	52 years/M	H	COPD, DM, HTN, CHF, CAD	5 days	RL: 1000 LL: 650 S: 260	Acute and chronic bronchitis w/square meter and interstitial inflammation, alveolar edema and focal hemorrhage, acute pneumonia
11	56 years/M	H	COPD, DCM, Cirrhosis	UNK	RL: 1000 LL: 560 S: 150	Acute and chronic bronchitis and interstitial inflammation, alveolar edema, organizing pneumonia with fibrin/hyaline membranes
12	59 years/F	H	COPD, DM, HTN, CAD, DCM, obesity	3 days	RL: 470 LL: 390 S: 550	Chronic tracheitis and interstitial inflammation, alveolar edema

H, Hispanic; C, Caucasian; NA, Native American; COPD, chronic obstructive pulmonary disease/emphysema; CAD, coronary artery disease; HTN, hypertension; CHF, congestive heart failure; DCM, dilated cardiomyopathy; DM, diabetes mellitus; RL, right lung; LL, left lung; S, spleen.

Autopsied Cases: Microscopic Features

The lungs in all cases revealed some degree of pulmonary interstitial inflammation: 5/12 cases (41.7%) were chronic only, whereas 7/12 cases (58.3%) had an additional acute component (Fig. 1*A*). The majority of cases (8/12; 66.7%) showed bronchopneumonia, characterized by an acute neutrophilic infiltrate (Fig. 1*B*). In two of the cases with bronchopneumonia, there were also fibrin strands and hyaline membranes indicating some degree of organization and fitting the picture of DAD (2/12; 16.7%) (Fig. 1*C*). The majority also demonstrated intra-alveolar edema (9/12; 75%); intra-alveolar hemorrhage occurred far less frequently (3/12; 25%) (Fig. 1*D,E*). Five cases (5/12; 41.7%) showed chronic bronchitis/bronchiolitis. Another five cases showed mixed acute and chronic bronchitis/bronchiolitis, while two (2/12; 16.7%) showed no inflammation whatsoever. Of those cases with acute and chronic bronchitis/bronchiolitis, three (3/12; 25%) also showed reactive squamous metaplasia of the respiratory epithelium (Fig. 1*F*).

The trachea was not sampled in four cases (4/12; 33.3%); in one instance, this was because of autopsy restrictions placed by decedent's family. Of those cases with tracheal sections, 7/8 (87.5%) revealed chronic tracheitis, while 1/8 (12.5%) showed denuded epithelium with no significant inflammation. The spleen was also not sampled in four cases: in cases that were sampled, 3/8 (37.5%) revealed depleted white pulp, 1/8 (12.5%) revealed follicular hyperplasia, and the remainder (4/8; 50%) appeared unremarkable.

Two cases were notable for their extra-pulmonary manifestations. In one case (case 5), a 6-year-old Native American female presented with fever, nausea/vomiting, and myalgia. An antemortem rapid influenza test was positive for Type A Influenza. The girl's disease course was short: she died the following day. At autopsy, in addition to her overall mild pulmonary findings, she was also discovered to have fulminant myocarditis (Fig. 2*A,B*). Sections from this case were sent to the CDC in consultation: no viral or bacterial antigens were identified in the myocardium.

In the second case (case 6), a 17-year-old Hispanic girl presented with headache and stiffening of extremities. An antemortem nasopharyngeal RT-PCR was positive for pH1N1. Again the disease course was short: she died the following day. At autopsy, postmortem nasopharyngeal RT-PCR was also positive. Grossly, the brain revealed edema as evidenced by flattening of gyri and narrowing of sulci. There were inferior cerebellar grooves indicating tonsillar herniation (Fig. 2*C*). Microscopically, there was mild parenchymal hemorrhage (especially in the medulla) consistent with tonsillar herniation. Amyloid precursor protein IHC highlighted a "wave-like" staining pattern consistent with ischemic injury in both the pons and medulla (Fig. 2*D,E*). Extensive additional brain as well as heart sections were submitted and revealed no evidence of meningitis, encephalitis, or myocarditis.

Discussion

This report presents the clinical and epidemiologic features of all fifty 2009 pH1N1 fatalities occurring in the state of New Mexico during 2009. In 12 of these cases, autopsies were performed. Our study reviews the histopathologic features of these fatalities and how they differ in certain key respects from those reported in other states. Previously published studies addressing pH1N1 influenza histopathology have reported acute and/or organizing DAD in the majority of autopsied cases (74–100%) (11–15). In our series, only 2/12 (16.7%) decedents manifested DAD. Also, in comparison with other reported fatalities, the majority of New Mexican autopsied fatalities had a relatively rapid disease course: time from onset of symptoms to death ranged from 1 to 12 days (median, 2 days) versus other series' range of 2–44 days (median, 7 days) and 1–44 days (median, 8 days) (9,11). These findings may indicate that New Mexican pH1N1 fatalities generally did not survive long enough to develop the more classic pulmonary manifestations. It is also notable that almost half of the autopsied New Mexican fatalities were children: 5/12 (41.7%) decedents were ≤6 years of age. The New York City Office of the Chief Medical Examiner reported only 3/34 (8.8%) decedents ≤15 years of age in their series of

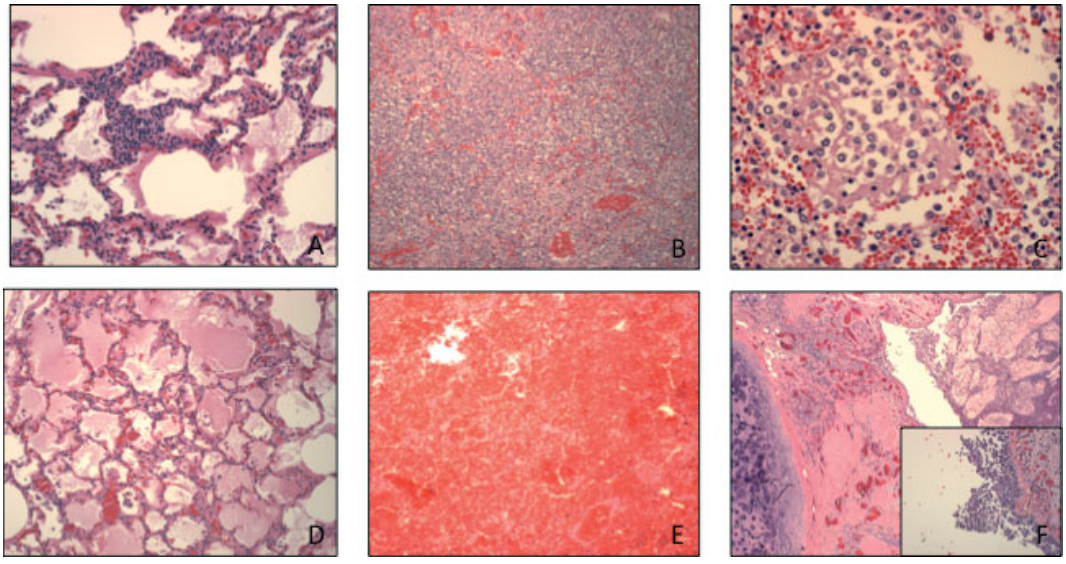

FIG. 1—*Pulmonary pathology in H1N1 fatalities. (A) Mixed acute and chronic interstitial inflammation distending alveolar septae, H&E 20×. (B) Acute diffuse bronchopneumonia, H&E 10×. (C) Early diffuse alveolar damage characterized by pink fibrin strands and hyaline membranes admixed with inflammatory cells, H&E 20×. (D) Intra-alveolar edema, either focal or diffuse, is among the most common findings, H&E 10×. (E) Intra-alveolar hemorrhage is also seen, H&E 10×. (F) Acute and chronic bronchitis. Inset shows squamous metaplasia of respiratory epithelium, H&E 10×, 20×.*

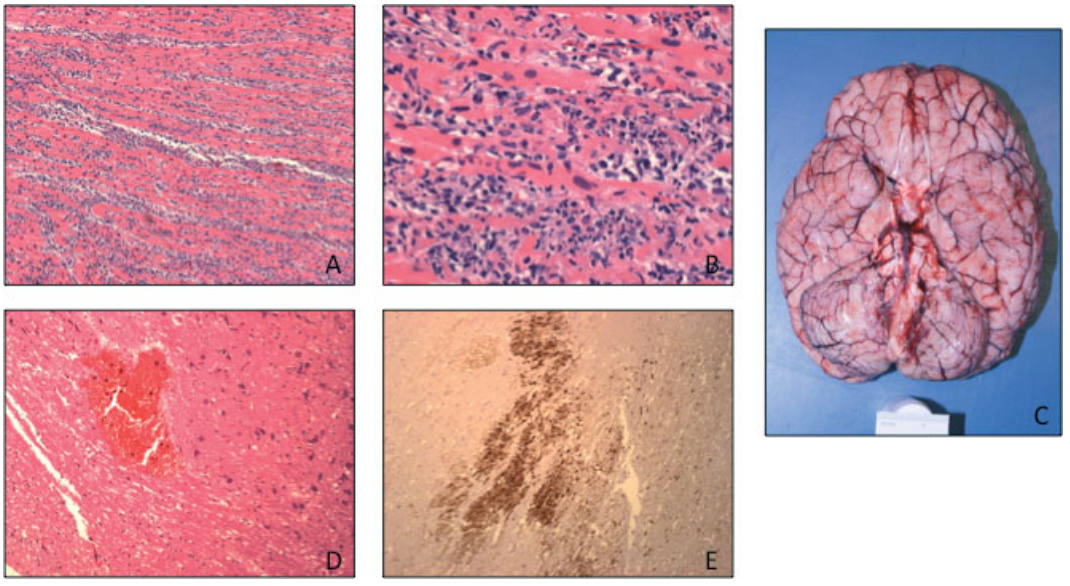

FIG. 2—*Extra-pulmonary pathology in H1N1 fatalities. (A,B) Case 5: Fulminant myocarditis characterized by neutrophilic infiltrate and apoptotic debris dissecting through myocardium, H&E 10×, 40×. (C) Case 6: Cerebral edema as evidenced by flattening of gyri and narrowing of sulci. Inferior cerebellar grooves indicating tonsillar herniation. (D) Medulla with mild parenchymal hemorrhage, H&E 10×. (E) Medulla and pons with "wave-like" staining pattern consistent with ischemic injury. Amyloid precursor protein immunohistochemical stain 10×.*

pH1N1 fatalities, and only one of these children had DAD at autopsy (1/3; 33.3%) (11). In a study of 2003–2004 pediatric seasonal influenza fatalities, there was also a lower incidence of DAD than that reported for adult pandemic fatalities, namely 26% (7). Infant and child immune systems are known to be less well-developed than those of adults. There are quantitative and/or qualitiative differences in antibody production, in T-cell subsets, and in cytokines (19). They may thus be less apt to develop advanced manifestations of influenza infection such as DAD. Larger studies addressing the histopathologic features of pediatric 2009 pH1N1 fatalities would be helpful in understanding fatal mechanisms.

In addition to DAD, other commonly reported histologic manifestations of pH1N1 virus infection include edema and inflammation of the trachea and bronchi, chronic interstitial inflammation and edema, acute pneumonia, alveolar hemorrhage, and pulmonary thromboemboli. Hemophagocytosis within paratracheal or hilar lymph nodes, as well as spleen and bone marrow, is also reported, though the incidence is variable (61–100%) (9,15). The most common histologic pulmonary findings in our series were alveolar edema (9/12; 75%), interstitial inflammation (100%), bronchitis/bronchiolitis (10/12; 83.3%), acute bronchopneumonia (8/12; 66.7%), and chronic tracheitis (7/8; 87.5%). In 3/12 (25%) cases with microscopically evident pneumonia, there was culture-proven bacterial co-infection. The likelihood of acquiring bacterial co-infection appears to correlate with survival interval, as two of these three cases had the longest survival times in our series, at 7 and 12 days, respectively.

Our study highlights the importance of the autopsy in tracking the epidemiology of infectious disease. In 9/12 (75%) cases, pH1N1 was not known to be the cause of death until after autopsy, and in three cases, autopsy was critical in establishing that pH1N1 infection was incidental rather than instrumental to death. Our office uses the Med-X surveillance strategy to identify potential fatal infectious disease cases for autopsy (20).

Our findings also demonstrate the importance of conducting a thorough microscopic examination of all major organs: while influenza virus generally results in the previously described pulmonary pathology, extra-pulmonary manifestations have also been reported. One of our pediatric fatalities demonstrated fulminant myocarditis. Myocarditis has been reported in association with pH1N1, as well as other influenza subtypes (21–24). It may be a more common phenomenon than previously suspected. For instance, in autopsied fatalities from the 1957 influenza pandemic, approximately one-third of cases revealed focal to diffuse myocarditis (23). In some instances, the virus has been successfully cultured from myocardium, while others remain culture-negative. The lack of consistent culture positivity suggests that the mechanism of influenza myocarditis may be autoimmune in nature (22). A second unique extra-pulmonary manifestation in our series was neurologic complications: an adolescent girl developed pH1N1-associated cerebral edema and subsequent tonsillar herniation. Neurologic complications have been reported in association with seasonal, as well as pH1N1 influenza (7,25). Specifically, complications have included seizures, encephalitis, encephalopathy, and rarely death. Diagnosis is usually carried out by means of respiratory samples, as the virus is only infrequently detected in the cerebral spinal fluid (CSF). In this case, the antemortem and postmortem nasopharyngeal samples were rtRT-PCR positive for pH1N1; no virus was isolated from the postmortem CSF, however. It is recommended that in cases of suspected pH1N1 infection with concurrent neurologic symptoms, antiviral treatment be administered promptly, without waiting for final results of diagnostic studies (25).

Native Americans comprised 11/50 (22%) of all New Mexico pH1N1 fatalities and 2/12 (16.7%) of autopsied cases. As the overall New Mexican population is only 9.6% Native American, Native Americans were disproportionately represented among the 2009 pH1N1 fatalities in our state (26). This trend has been reported in other U.S. states with the most recent pandemic, as well as historically. In the 1918 influenza pandemic, fatality rates in North American aboriginals were also higher than that of nonaborginals: 3–9% versus <0.75% (27). In the 2009 pandemic, Native Americans/Alaskan natives in the United States had an influenza mortality rate four times higher than all other racial groups combined (28). Factors that have been suggested to account for this include remote rural locations and poverty resulting in delayed/decreased access to healthcare, higher prevalence of underlying medical

comorbidities, and possibly unrecognized genetic predisposition (1,28). In our series, Native Americans did not have an appreciably greater number of comorbidities than did other races in New Mexico, but did have higher rates of obesity. Overall, the prevalence and type of comorbidities seen in New Mexican adult fatalities resembled those reported nationwide: hypertension (37.5%), diabetes (32.5%), chronic obstructive pulmonary disease (COPD)/emphysema (27.5%), cirrhosis (17.5%), asthma (15%), coronary artery disease (15%), congestive heart failure (15%), and malignancy (12.5%) (1,27,29). Eighty-five percent of non-Native American adults had at least one comorbidity as compared to 75% of Native American adults, and in most cases comorbidities were multiple. Obesity has been proposed as a novel risk factor for increased pH1N1 influenza morbidity and mortality (1,29). In our series, 20% of adults and 40% of children were obese. A greater percentage of Native American fatalities were obese than other races: 36.4% (4/11) versus 20.5% (8/39). Overall, these findings indicate that efforts to improve influenza vaccination and antiviral therapy, as well as to better elucidate reasons for increased pH1N1 mortality among Native American populations, are needed.

Gastrointestinal (GI) symptoms appear to be more common in pH1N1 viral infections than in seasonal influenza. In one major series, more than one-third of adults who were hospitalized and/or died of pH1N1 complications reported nausea and vomiting, and one-fifth reported diarrhea (29). In our series, the reported incidence of GI symptoms was similarly higher than those with seasonal influenza: 11/50 (22%) reported nausea and/or vomiting, while 6/50 (12%) reported diarrhea. Pandemic H1N1 virus has been detected in the stool of infected patients. Furthermore, it has been shown to replicate more efficiently in intestinal cells than does seasonal H1N1, which likely accounts for the increased incidence of GI symptoms (6). Anecdotally, three of the decedents in our series were reported to have a several-hour period of symptom remission/apparent recovery prior to death. We have not seen this trend reported in any of the current pH1N1 literature, and its significance is uncertain.

In conclusion, although DAD has been reported as a prominent histopathologic feature in 2009 pH1N1 fatalities, it was not commonly seen in New Mexico autopsies. In cases of decedents with very short intervals between onset of symptoms and death, pathologists should be aware that pulmonary manifestations of disease may be more subtle than previously reported, consisting mainly of interstitial inflammation, edema, tracheobronchitis, and focal acute bronchopneumonia. Extra-pulmonary manifestations of 2009 pH1N1 infection, such as myocarditis and cerebral edema/herniation, were seen in our series and should be ruled out by taking a thorough histologic sampling at autopsy. This is particularly important as virus often cannot be cultured from the CSF or myocardium. Certain demographic groups, such as Native Americans, have a higher risk of fatal outcome with pH1N1 infection, suggesting that autopsy (or at least external exam with procurement of nasopharyngeal viral cultures) should be aggressively pursued in cases of a suspected infectious disease death in this population. Autopsy pathologists play a critical role in identifying populations at risk of fatal complications from infectious disease, as well as elucidating the mechanisms by which viruses cause death.

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