ORIGINAL ARTICLE

Humidifier Disinfectant–associated Children's Interstitial Lung Disease

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Abstract

Rationale: Beginning in 2006, epidemics of a fatal lung injury of unknown cause in children were observed in Korea every spring. A recent study demonstrated that this type of children's interstitial lung disease (chILD) is associated with humidifier disinfectant use.

Objectives: To determine the clinical characteristics of this type of chILD and to assess whether the nationwide suspension of humidifier disinfectant sales in the autumn of 2011 affected its incidence.

Methods: The clinical characteristics of suspected cases between 2006 and 2011 were determined by a nationwide retrospective study. The potential causal relationship with humidifier disinfectants was examined by a prospective surveillance study after humidifier disinfectant sales were suspended.

Measurements and Main Results: In total, 138 children were diagnosed with this type of chILD, which was characterized by rapid progression, high mortality, predominance in the spring season, and a familial tendency. The annual incidence increased in 2011 and then dropped to zero in 2012. The children were on average 30.4 months old. The most frequent symptoms at admission were cough and dyspnea. As the disease progressed, the typical complication was spontaneous air leak. Eighty children (58%) died. Two years after humidifier disinfectant-sale suspension, no more new cases were found.

Conclusions: This study suggests that humidifier disinfectant inhalation causes an idiopathic type of chILD that is characterized by spontaneous air leak, rapid progression, lack of response to treatment, and high mortality. Further safety studies must be performed on common environmental compounds, particularly those that enter the human body by an unusual route.

Keywords: disinfectant; interstitial lung disease; chILD

At a Glance Commentary

Scientific Knowledge on the Subject: Starting in 2006, epidemics of a unique form of interstitial lung disease that largely occurred in spring were observed in Korean children. Their cause was unclear.

What This Study Adds to the Field: This study is the nationwide report of humidifier disinfectant–associated interstitial lung disease in children. Exposure to environmental chemicals through an unexpected route may be a potential hazard to human health.

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Children's interstitial lung disease (chILD), also known as pediatric diffuse lung disease, is a diverse group of rare lung diseases that are associated with high morbidity and mortality (1, 2). Recently, the diagnosis and classification of these diseases was significantly revised (3–5). In 2006, several cases of a particular type of chILD were observed in Korean children. It was characterized by acute abnormal gas exchange, diffuse radiologic findings that indicated ILD, and a poor prognosis (6–8). Additional cases emerged in the following years, where these patients initially had mild respiratory symptoms and progressed into acute respiratory distress or respiratory failure, some patients with spontaneous pneumothorax or pneumomediastinum. Significantly, these cases mainly occurred in spring. Furthermore, several cases showed that other family members also developed a similar illness around the same time (8–10). It was considered to be an idiopathic form of chILD that might have been caused by as yet unidentified microorganisms or inhalants in the ambient air that were largely present in winter and spring.

This notion was supported by a report published in November 2011 by the Korea Centers for Disease Control and Prevention (KCDC), which disclosed that there had been a spring outbreak of a lethal lung injury of unknown etiology in pregnant women in Korea (11). An epidemiologic study and an animal study indicated that it was highly likely that this lung disease was caused by the use of humidifier disinfectants (9, 11–13). Because the lung disease in these adult patients was clinically, radiologically, and pathologically very similar to the lung disease seen in the idiopathic form of chILD cases (6–8, 10), we performed a case-control study to determine whether there was also an association between humidifier disinfectants use and the risk of this form of chILD. Indeed, humidifier disinfectant use was shown to independently increase the risk of chILD (13).

Humidifiers are used to maintain a comfortable level of indoor humidity. However, if humidifiers are not cleaned regularly and thoroughly, germs, molds, and algae can grow in the water tanks and be dispersed into the environment by the humidifier, thus elevating the risk of inhaling these microorganisms (14). White dust inhalation is also increased by the use of unclean humidifiers (15). To prevent the growth of microorganisms, humidifier disinfectants are placed in humidifier water tanks. These disinfectants contain oligo (2-[2-ethoxy] ethoxyethyl) guanidium chloride (PGH), polyhexamethyleneguanidine (PHMG), 5-chloro-2-methylisothiazol-3 (2H)-one/2-methylisothiazol-3-one (MIT), and didecyldimethylammonium chloride (DDAC) (9, 16). They first entered the market in Korea in 1994 and more than 20 products were available just before their sale was suspended in the autumn of 2011 after the KCDC report (17). A cross-sectional study performed in 2011 revealed that one-third of the Korean population had used a humidifier and that half of them used humidifier disinfectants (18, 19). Humidifier use was particularly prevalent in winter.

The aim of the present retrospective nationwide multicenter study was to determine the clinical characteristics of this form of chILD in Korean children that was characterized by radiologic findings of diffuse ILD and a predominant spring occurrence. In addition, because humidifier disinfectant sales were suspended in the autumn of 2011, it was possible to perform a postinterventional prospective study to determine whether the ban affected the incidence of this type of chILD.

Methods

Study Design

After the August 2011 KCDC report of the humidifier disinfectant-induced lung injury in pregnant women, nationwide retrospective and prospective surveillance studies of the spring-related form of chILD in Korea were performed (*see* Appendix 1 in the online supplement).

Retrospective Study

The 84 secondary general hospitals and tertiary medical centers that are the base hospitals that represent all regions of Korea participated in this study. To identify the cases of interest, the same working definition used in our previous case-control study of humidifier disinfectant–associated chILD was used (13). In brief, the hospitalized patients had to (*1*) be 18 years of age or less; (*2*) show rapidly progressive respiratory distress; and (*3*) demonstrate radiologic evidence of diffuse or centrilobular ground-glass opacities and/or air leak syndrome, such as pneumothorax, pneumomediastinum, or subcutaneous emphysema. The study period was between January 2006 and September 2011: this reflects the fact that this type of chILD was first recognized in 2006 and the ban on humidifier disinfectants was introduced in the autumn of 2011 (6). To obtain the data of cases that met the inclusion criteria, case

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report forms by the nationwide network of the Korean Academy of Pediatric Allergy and Respiratory Disease (KAPARD) between October and December 2011 were sent to all pediatric pulmonologists in secondary and tertiary hospitals throughout the country.

The case report forms, radiologic images, and biopsy specimens of 160 suspected cases from 27 centers were collected and analyzed. Each case report form included the demographic data; family history; and detailed clinical information regarding the respiratory symptoms, physical examination, response to treatment, clinical outcome, and laboratory findings including complete blood cell count, blood gas analysis, and culture studies. Simple chest radiograph and computed tomography images were obtained from all patients. In the 61 patients who underwent open lung biopsy or autopsy, biopsy specimens were also collected. Thereafter, the task force team, which consisted of six pediatric pulmonologists, two radiologists, and two pathologists, reviewed all collected data for all suspected cases, including the radiologic and pathologic findings. Finally, 138 children who met the inclusion criteria (13) were selected for this study.

This retrospective study was approved by the institutional review boards of Asan Medical Center, Severance Hospital, Samsung Medical Center, and Seoul National University Hospital. The written consent requirement was waived.

Prospective Study

If humidifier disinfectant use was indeed the cause of this fatal, seasonal type of chILD, such cases would disappear after the sale of these disinfectants was suspended in 2011. To test this, we established a real-time nationwide reporting system by KAPARD throughout the country in 2011 so that all new suspected cases that met our working definition could be reported. Thus, the same 84 secondary general hospitals and tertiary medical centers that participated in the retrospective study were selected. In addition, eight medical centers representing each of the eight provinces of Korea were designated as local centers. A pediatric pulmonologist in each local center was elected to be the coinvestigator in the prospective study. Under this reporting system, the 84 network hospitals reported the occurrence of new suspected cases to their local center in real-time. In addition, no new cases were also reported every month.

The institutional review boards of each institute approved this prospective study. Written consent was required for all patients who were identified after the suspension of humidifier-disinfectant sales.

Results

Epidemiology of the chILD

The annual incidence with 95% confidence intervals (CIs) was calculated by using Poisson distribution. The annual incidence rates (per 1,000,000 persons) were 2.447 (95% CI, 1.532–3.708) in 2006, 2.178 (1.311–3.401) in 2007, 1.178 (0.564–2.168) in 2008, 1.579 (0.840–2.702) in 2009, 2.884 (1.826–4.329) in 2010, and 6.563 (4.883–8.630) in 2011. In 2012, after the autumn 2011 intervention, the incidence dropped dramatically to 0 (0–0.53). Most of the cases in the study period (99 cases, 71.7% of the whole cohort) occurred in the spring season: 23 cases (16.7% of the whole cohort) developed in March, 42 (30.4%) developed in April, and 34 (24.6%) developed in May (Figure 1; *see* Appendix 2A).

Clinical Characteristics

Table 1 shows the clinical characteristics of the patients. The children were on average 30.4 months old (*see* Appendix 2B for distribution of the ages). The male-to-female ratio was 1.3:1. The most frequent symptoms at admission were cough (95.7%), tachypnea or dyspnea (75.4%), sputum (51.4%), chest wall retraction (47.4%), and fever (26.1%). The disease course started with mild respiratory symptoms that rapidly progressed to respiratory distress or respiratory failure. The median duration of cough before admission was 21 days. Most of the patients were previously healthy: only 10.1% of patients had an underlying disease, such as asthma. In 26 (18.8%) of the cases, one or more family members (siblings or parents) manifested similar symptoms and radiologic and pathologic abnormalities around the same time as the index case.

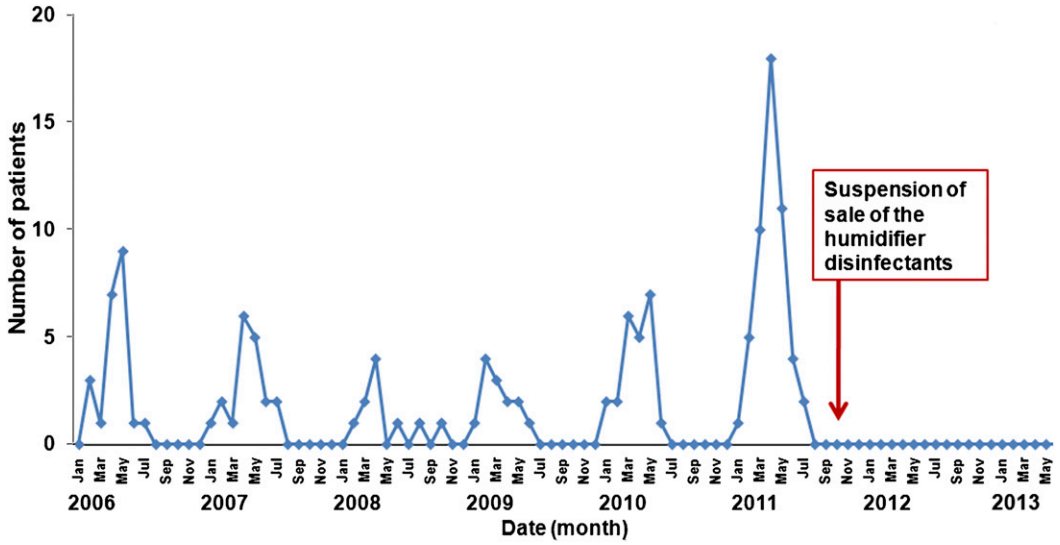

Figure 1. Monthly distribution of the occurrence of humidifier disinfectant–associated children's interstitial lung disease between 2006 and 2013. It should be noted that new cases were not detected after humidifier disinfectant sales were suspended.

Table 1: Clinical Characteristics of Patients with Humidifier Disinfectant–associated Children's Interstitial Lung Disease (N = 138)

Values	N (%)
Age, mo (range)	30.4 (2–125)
Sex, male	78 (56.5)
Symptoms and signs at admission	
Cough	132 (95.7)
Tachypnea or dyspnea	104 (75.4)
Sputum	71 (51.4)
Chest wall retraction	65 (47.4)
Fever	36 (26.1)
Rhinorrhea	34 (24.6)
Nasal flaring	33 (24.3)
Cyanosis	32 (23.5)
Underlying diseases	
Chronic bronchitis	1 (0.7)
Asthma	4 (2.9)
Other allergic diseases	7 (5.1)
Cardiovascular disease	1 (0.7)
Autoimmune disease	1 (0.7)
Family history of acute lung injury similar to the patient	
Yes	26 (18.8)
Pa_{O_2}/FI_{O_2} at admission (n = 114)	
<200	66 (57.9)
200–299	34 (29.8)
$\geqslant 300$	14 (12.3)
Treatment for respiratory insufficiency or failure	
Oxygen supplementation	122 (88.4)
Ventilator care	78 (56.5)
Extracorporeal membrane oxygenation	25 (18.1)
Lung transplantation	1 (0.7)
Outcomes	
Mortality	80 (58.0)

Data were expressed as mean (min–max range) or n (%).

Radiologic Findings

As shown in Table 2, the radiologic findings from the simple chest radiograph at admission were ground-glass opacity (57.2%), consolidation (43.5%), pneumomediastinum (30.4%), and pneumothorax (15.2%). Initial chest radiographs in most cases showed ground-glass opacity or irregular patchy opacity, which later progressed to diffuse dense consolidation or ground-glass opacity involving the whole lung. Spontaneous air leak occurred frequently during disease progression. During the disease course, pneumomediastinum and pneumothorax developed in 59.4 and 55.8% of the patients, respectively (data not shown). Figure 2 shows the radiologic findings of representative cases, which are the initial phase (Figure 2A), advanced phase (Figure 2B), and the late phase (Figure 2C), and one severe case (Figure 2D).

Laboratory Findings

Table 3 lists the laboratory features of the patients. The median leukocyte count was 13,201 per microliter, the median erythrocyte sedimentation rate was 20.7 mm/h, and the median C-reactive protein level was 1.5 mg/L. Although viruses were not detected in the nasopharyngeal aspirate of most patients (79.8%), a few patients had rhinovirus, parainfluenza, respiratory syncytial virus, influenza virus, adenovirus, and coronavirus in their nasopharygeal aspirate. Only a few patients had positive bacterial culture results from the sputum (8.2%) or blood (2.4%). Most patients underwent various laboratory investigations to exclude disorders, such as aspiration syndrome, primary pulmonary hypertension, or immunologic or rheumatologic disorders. These investigations did not yield any abnormal findings. Thus a consistent etiology or underlying disease that predisposed the patient to respiratory distress could not be identified.

Histopathologic Findings

Lung biopsy was performed in 60 (43.5%) patients and autopsy in one patient. The common pathologic features were variable degrees of bronchiolar injury that was accompanied by a bronchiolocentric acute lung injury pattern (Figure 3A). The bronchiolar lesion varied from simple mononuclear cell infiltration to necrotizing bronchiolitis (Figure 3B) and obliterative bronchiolitis (Figure 3C, *arrow*). The parenchymal lesion was identical to diffuse alveolar damage except for its pattern of distribution: the alveolar damage was predominantly observed in centrilobular areas with relative sparing of the lobular periphery. The alveolar septal structures were widened by mononuclear cell infiltration and/or fibroblastic proliferation. Granulomatous lesions or old mature fibrosis, including smooth muscle metaplasia and microscopic honeycomb, were not observed. In most cases, the fibroinflammatory process was temporally homogeneous. In many of the cases, foamy histiocyte accumulation was observed in the alveolar spaces of the peribronchial regions (Figure 3C, *asterisk*). In most areas, alveolar pneumocytes were replaced by type II cells or activated large cells. Intraalveolar fibroblastic plugs that indicate organizing pneumonia patterns were detected frequently (Figure 3D).

In early lesions, the bronchiolar epithelium was denuded or replaced by flattened epithelium; this was accompanied by mild subepithelial fibroblastic proliferation. The alveolar septal architecture was relatively well-preserved, although the inflammatory infiltration-

Table 2: Simple Chest Radiograph Findings at Admission in Patients with Humidifier Disinfectant–associated Children's Interstitial Lung Disease (N = 138)

Values	N (%)
Normal	5 (3.6)
Abnormal	132 (95.7)
Ground-glass opacity	79 (57.2)
Consolidation	60 (43.5)
Pneumomediastinum	42 (30.4)
Peribronchial infiltration	27 (19.6)
Pneumothorax	21 (15.2)
Subcutaneous emphysema	16 (11.6)
Emphysematous lung	3 (2.2)
Pleural effusion	1 (0.7)
Unknown	1 (0.7)

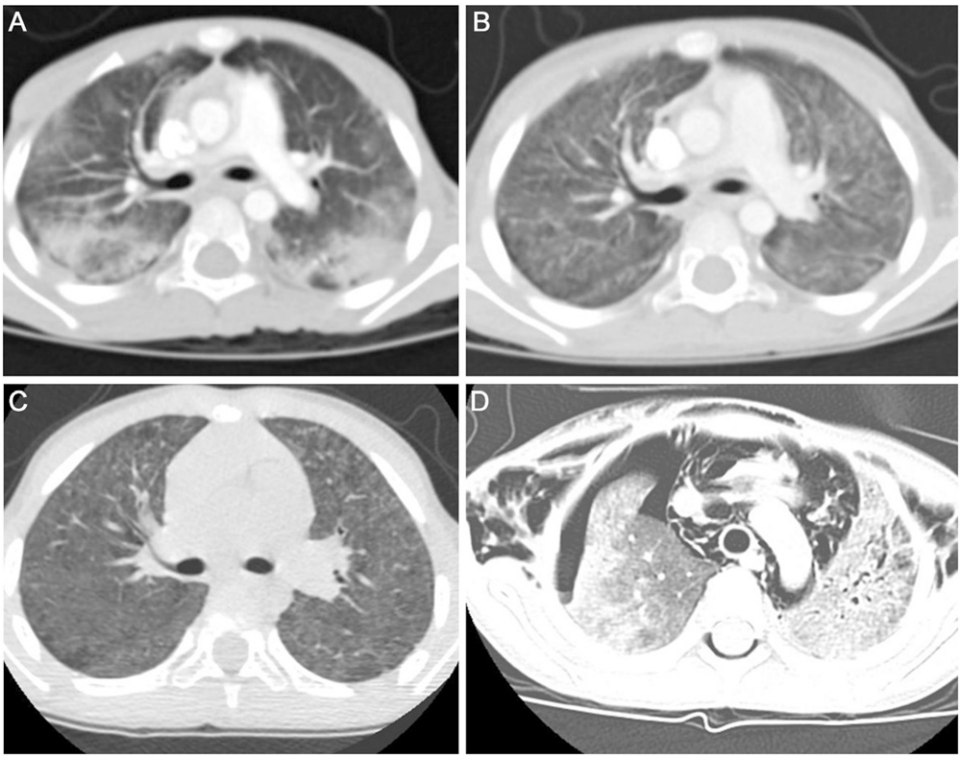

Figure 2. Radiologic findings of representative cases of humidifier disinfectant–associated children's interstitial lung disease. (*A*) Chest computed tomography (CT) performed 3 weeks after symptom onset showed multifocal patchy consolidation and peribronchial infiltration with subpleural sparing. (*B*) After 1 month of follow-up, the chest CT scan showed diffuse centrilobular ground-glass attenuation with the disappearance of the consolidation. (*C*) Chest CT of the patient after 1 year showed diffuse centrilobular nodules with ground-glass opacities, which are consistent with diffuse centrilobular fibrosis. (*D*) In a 5-year-old girl with a severe disease course, the chest CT scan showed extensive pneumomediastinum, pneumothorax, and subcutaneous emphysema.

induced septal thickening varied in severity with relative restriction to the peribronchiolar regions. The subpleural and paraseptal airspaces were relatively well-preserved, even in the lungs, at the early stage of the lesion. The late phase was characterized by the centrilobular distribution of parenchymal remodeling caused by septal inflammation, fibroblastic proliferation, collagen deposition, and intraalveolar fibroblastic plugs with mural incorporation. The bronchioles were severely damaged and exhibited scarring. The ring fibrosis that occurs in end-stage diffuse alveolar damage was not identified (*see* Appendix 3).

Outcomes

Of the 138 children, 80 (58.0%) died (Table 1). The mean length of stay in hospital of the 58 survivors was 38.4 days (range, 5–156 d). Seventeen of the surviving patients (29.3%) received critical care in the intensive care unit; their mean duration of hospitalization was 72.1 (1–535) days. Because survivors had got better after hospital discharge, they are doing well without any symptoms, oxygen use, or known ongoing pulmonary morbidity. Most patients (88.4% of the whole cohort) required oxygen supplementation: indeed, more than half of the cohort (56.5%) had ventilatory support because their Pa_{O_2}/Fi_{O_2} ratio was less than 200 (Table 1). Most of the patients received antiinflammatory therapy, including glucocorticoids and other immunomodulatory drugs, such as hydroxychloroquine or cyclophosphamide. Treatment with antibiotics, antiviral agents, or antiinflammatory drugs failed in most patients. The mortality rate did not correlate with the severity of lung injury at admission (*see* Appendix 4).

Occurrence of New Suspected Cases after Intervention

After suspension of humidifier disinfectant sales, pediatric pulmonologists who belonged to the nationwide network of KAPARD were charged shortly thereafter to identify any new suspected cases that met the working definition. However, no new cases were reported in the 2 years after the suspension of humidifier disinfectant sales (Figure 1).

Discussion

In this study, all cases shared several common clinical characteristics: a rapid progression, high mortality, lack of response to treatment, and predominance in the spring season and in early childhood. There was also a familial association: in many cases, other family members, who were of different ages, also suddenly developed the same type of lung injury at the same time. The radiologic images frequently revealed diffuse centrilobular ground-glass opacity, often with spontaneous air leak. The histopathologic results were suggestive of an inhalation injury. Similar findings were observed in 2011 in pregnant women

Table 3: Laboratory Findings at Admission in Patients with Humidifier Disinfectant–associated Children's Interstitial Lung Disease (N = 138)

	Values
Peripheral blood leukocyte count/μl (n = 133)	13,201 (2,500–36,420)
Absolute lymphocyte count	4,107 (304–23,040)
Absolute neutrophil count	8,025 (550–28,080)
ESR, mm/h	20.7 (2.0–62.0)
CRP, mg/dl	1.5 (0–35.4)
Respiratory virus from nasopharyngeal aspirate (n = 114)	
Rhinovirus	9 (7.9)
Parainfluenza	5 (4.4)
Respiratory syncytial virus	4 (3.5)
Influenza	3 (2.6)
Adenovirus	1 (0.9)
Coronavirus	1 (0.9)
No detection	91 (79.8)
Bacteria from sputum culture (n = 85)	
Positive	7 (8.2)
Blood culture (n = 127)	
Positive	3 (2.4)

Definition of abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.
Data were expressed as mean (min–max range) or n (%).

with lethal lung injury that was associated with the use of humidifier disinfectants. Significantly, the present study also showed that after the sale of humidifier disinfectants was suspended in November 2011, new cases of this type of chILD were no longer detected.

To identify the characteristics and risk factors of this distinct type of chILD in Korea, which occurred every spring since 1995, we took a step-wise approach: we first performed a case-series study (8) and then a case-control study (13). Briefly, the case-series study showed that the disease had distinctive radiopathologic characteristics and was associated with rapid progression and high mortality. The 1:3 matched case-control study consisted of 16 cases and showed that the use of humidifier disinfectants was associated very strongly with an elevated risk of chILD. However, these two studies had inherent limitations: both were retrospective studies that were conducted in a single medical center. This limited the generalizability of the observations to the general population. To overcome this limitation, we conducted the present nationwide, real-time reporting system, which included the entire Korean pediatric population. As a result, it is highly likely that the use of humidifier disinfectants was one of the main causes of chILD in the whole Korean population, particularly because new cases did not arise

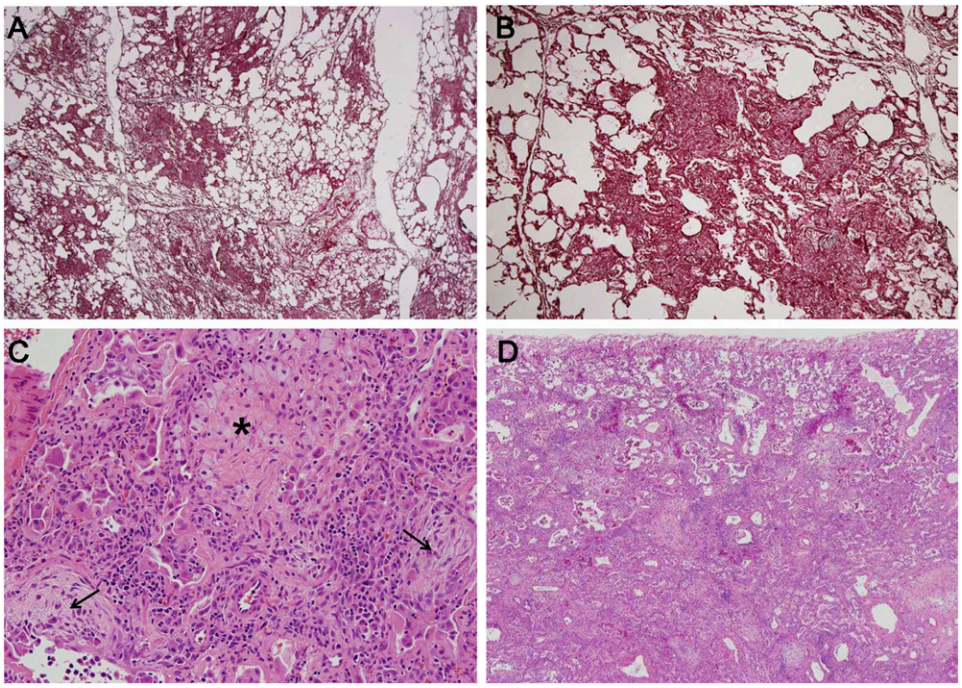

Figure 3. Pathologic findings of representative cases of humidifier disinfectant–associated children's interstitial lung disease. (*A*) A few pulmonary lobules are affected by interstitial thickening and fibrosis; this is predominantly observed in the centrilobular area (periodic acid Schiff silver, original magnification ×4). (*B*) The typical bronchiolocentric destruction was observed (periodic acid Schiff silver, original magnification ×40). (*C*) Alveolar septa and bronchioles (*arrows*) are damaged by inflammatory infiltration and fibroblastic proliferation. Collapsed alveolar spaces are lined by activated pneumocytes and filled with foamy histiocytes (*asterisk*) (hematoxylin and eosin, original magnification ×200). (*D*) In the advanced phase, most of the airspaces are lost because of extensive interstitial thickening and fibrosis. The centrilobular distribution is suggested by the relative sparing of subpleural parenchyma (hematoxylin and eosin, original magnification ×40).

after the ban of humidifier disinfectants. Although the causal relationship remains indirect because of ethical issues and low incidence of chILD, with our well-structured real-time reporting system, we were able to present valuable and reliable evidence. In addition, in the future, through our real-time reporting system, it is possible to recognize such epidemics early.

Approximately 20% of the cases in the present study had a familial connection. Previous reports of other forms of chILD have identified lower rates of familial cases (3, 20). For example, in idiopathic pulmonary fibrosis, only 0.5–2% of cases showed a familial connection (21). Several genetic mutations (e.g., in ATP-binding cassette transporter A3, telomerase, and surfactant protein C) seem to play a key role in idiopathic pulmonary fibrosis pathogenesis (22, 23). Although there are also some forms of familial lung diseases, the temporal nature of presentation in the family members in this study suggests they were exposed to the same causative agent in the environment. Thus, the burden of environmental exposure together with genetic modifiers may explain why some children developed chILD but others did not.

A close analysis of potential environmental agents revealed that this form of chILD was probably not caused by a microorganism that was spread in a seasonal epidemic fashion: culture studies and biopsies failed to detect any specific and consistently present microorganism (6, 7). Although the possibility of an as yet unknown virus or of a triggering role of nonspecific infection could not be excluded, this form of chILD has presented unique and consistently clinical-radiologic-histopathologic features regardless of the presence of microorganisms. Especially, the histopathologic findings from our patients (which demonstrated that the lung injury was caused by the inhalation route [8]) and the absence of new cases after the suspension of humidifier disinfectant sales strongly suggest that the chILD cases seen in the present study were caused by the use of humidifier disinfectants. Although two similar cases were reported by the real-time reporting network during our prospective study, the task force team concluded that these cases did not meet the definition of this type of chILD. One case was diagnosed with a severe form of bronchiolitis obliterans caused by *Mycoplasma pneumoniae* infection, whereas the other case was diagnosed with massive aspiration syndrome with aspiration pneumonia.

This notion is further supported by the spring predominance of the chILD (*see* Appendix 2A) and the fact that a cross-sectional study in Korea revealed that people use humidifiers and humidifier disinfectants most frequently in the winter season; this is also when they spend the most time indoors (18). Given this clustering of cases in spring, we hypothesized that dose-dependent exposure and/or host susceptibility may explain the rare occurrence of the chILD among the numerous humidifier disinfectant users. The age distribution of the patients in the present study further supports this notion: whereas the mean age of the patients (30.4 mo) was similar to or older than the age of most patients with chILD (24, 25), most of our patients were between 1 and 2 years old and very few were older than 6 years (*see* Appendix 2B). This may reflect the fact that young children are generally exposed to higher levels of humidifier disinfectant than adults because they spend more time on average in the home. Moreover, young children may be more vulnerable to environmental toxic inhalants than older children or adults because of their immature lung physiology and their larger lung surface relative to body weight (18, 19).

Humidifier disinfectants contain PGH, PHMG, 5-chloro-2-methylisothiazol-3 (2H)-one/MIT, or DDAC (9, 16). PGH, PHMG, and MIT are widely used as disinfectants or preservatives in cosmetics, water systems, and swimming pools. Thus, their use is subject to oral intake and skin contact safety regulations (26, 27). However, their inhalation toxicity and ability to induce lung injury have not been fully evaluated. An *in vivo* study showed that intratracheal instillation of DDAC in mice resulted in dose-dependent inflammatory changes in the bronchoalveolar lavage fluid that were accompanied or followed by pulmonary fibrosis (12). Another study reported that intratracheal instillation of DDAC alters the pulmonary immune defense system of mice and thereby may promote susceptibility to infection (16). Notably, several viruses were detected in some of the patients in the present study: it is possible that humidifier disinfectant use could promote the lung injury induced by certain viruses. A recent study showed that the treatment of zebrafish with PGH and PHMG resulted in acute cardiovascular toxicity that was associated with severe inflammation, atherogenesis, and aging (28). Finally, our retrospective case-control study showed that humidifier disinfectants independently increased the risk of chILD in spring (13). These observations together are concerning: tens of thousands of synthetic environmental chemicals have been invented and used over the last few decades to improve the convenience of daily life but although some have been shown to be hazardous for the human body, only a few have been fully evaluated (29). It should be noted that the incidence of chronic pediatric diseases during the same period as the explosion in synthetic chemical use has also increased (30).

The most common and earliest noticeable symptom of this form of chILD described in the present study was cough. This is a nonspecific symptom of most respiratory diseases, which means that it was difficult to diagnose this chILD in the early stage. The median duration of symptoms before admission was 21 days, which indicates that it is an acute or subacute condition. By contrast, other types of chILD have a more chronic course: the average duration from the onset of symptoms to the time of diagnosis is several months (3–5). The second most prominent symptom and sign of the chILD reported in the present study was respiratory difficulty, mainly tachypnea. These symptoms progressed rapidly despite treatment with medications, such as antibiotics, antiviral agents, or antiinflammatory agents. Spontaneous air leak during the clinical course was common and the patients frequently required oxygen supplement or ventilatory support. Although the aggressive clinical course and radiologic findings of the chILD reported here are similar to those of acute interstitial pneumonia (31), this form of chILD is characterized by unique pathologic patterns of fibrosis in the bronchioles that are not observed in acute interstitial pneumonia or other chILDs (5, 8, 10). Based on the classification of the various chILDs (4) and exposure-related ILD (20), the lung disease described in the present study can be categorized as environmental agent-related chILD in relationship to other causes, which may have a similar clinical presentation. The

notable damage pattern with the concomitant presence of centrilobular destruction with peribronchiolar and parenchymal damage along the respiratory tract would be an important clue to humidifier disinfectant–associated chILD, even though it is not clear whether the radiographic and histopathologic findings are specific to the etiology of this lung disease: bronchiolitis obliterans and other toxic chemical inhalation–associated ILDs have different damage patterns (32, 33). The radiologic finding that our patients lacked heterogeneous air-trapping also distinguishes this chILD from the popcorn lung that is caused by inhalation of diacetyl (34).

The present study had a few limitations and some uncertainty about the association of the chILD with environmental agents persists. First, we could not confirm that all patients used humidifier disinfectants because our study was retrospective. In addition, it was not possible to evaluate the exact concentration or duration of exposure, even in the patients who had clearly been exposed to humidifier disinfectants. Second, we cannot explain why some individuals were more prone to chILD than others (18, 19). Little is known about differences in individual susceptibility to environmental toxic inhalants. Lastly, it remains possible that a mild type of humidifier disinfectant–associated chILD exists. Mild cases could not be detected by the present study because our working definition of the chILD focused on the moderate to severe cases. It is necessary to determine the whole spectrum of this disease, including the mild phenotypes.

In conclusion, the present study suggests that inhalation of humidifier disinfectants causes an idiopathic type of chILD that is characterized by spontaneous air leak, rapid progression, lack of response to treatment, and high mortality. Thus, in cases of unusual disease progression with no response to treatment, an environmental hazard should be suspected, especially one that is introduced by an unexpected route. ■

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