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Chronic Lung Disease Secondary to Ammonia Inhalation Injury: A Report on Three Cases

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Inhalation of highly hydrosoluble toxicants, like ammonia, can be associated with chronic lung diseases, which have been partially characterized. We present the cases of three patients who were evaluated 2 years after massive exposure to ammonia in occupational settings. They presented with chronic dyspnea, and clinical pictures consistent with restrictive lung dysfunction, obstructive lung disease, and bronchial hyper-reactivity and small airways disease, respectively. The findings in 94 reported cases of inhalation injury due to massive exposure to ammonia are reviewed; in 35 cases follow-up for at least 1 year was available. The range of chronic pulmonary diseases associated with ammonia inhalation injury is reviewed, and suggestions for appropriate diagnostic evaluation are made.

KEY WORDS: ammonia, lung diseases, occupational diseases, asthma

INTRODUCTION

Overexposure to ammonia in the occupational setting can be associated with a range of anatomic and functional abnormalities of the respiratory tract that have been sporadically reported in the medical literature [Slot, 1938; Caplin, 1941; Brille et al., 1957; Lepine and Soucy, 1962; Derobert et al., 1964; Levy et al., 1964; Sestier et al., 1969; Kass et al., 1972; Walton, 1973; Sobonya, 1977; Close et al., 1980; Hoeffler et al., 1982; Flury et al., 1983; Bernstein and Bernstein, 1989; Leduc et al., 1992]. In those who survive an acute episode, the injury to the respiratory tract can result in disabling chronic pulmonary disease. In this paper we describe the cases of three men who were all evaluated approximately 2 years after exposure to large amounts of ammonia in occupational settings. They all presented with complaints of persistent respiratory symptoms, which in some cases are known to elude firm characterization by routine testing [Close et al., 1980; Walton, 1973]. After describing their clinical presentation, we discuss the different diagnostic means available to assess the long-term anatomic and physiopathological consequences of inhalation injuries.

CASE REPORTS

Case 1

Mr. A was a 30-year-old Afro-American man who was referred for evaluation in June 1983, 2½ years after his exposure to a high concentration of anhydrous ammonia gas at a transportation equipment factory where he worked as an engine testing operator. The gas leaked from a refrigeration system in a room next to the one where he was working. He immediately noted burning of his eyes, upper airways, and skin, as well as cough and pleuritic chest pain. He tried to assist another employee, and he estimated his exposure duration to be approximately 15 min. He was admitted to a local hospital, where he was noted to have conjunctivitis and rhinopharyngitis. The chest radiograph was normal, and the resting room air arterial blood gas revealed a pH of 7.39,

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TABLE I. Pulmonary Function Tests in Three Patients Exposed to High Concentrations of Ammonia

Case no.	No. 1		No. 2	No. 3	
Date (age, yr)	10/78[1] (22)	06/83 (27)	08/89 (30)	08/91[1] (45)	11/92 (46)
FEV_1, l/s	4.20 (109%)	2.82 (73%)	1.44 (41%)	4.17 (99%)	4.25 (101%)
FVC, l	4.70 (100%)	3.66 (78%)	2.78 (63%)	5.23 (101%)	5.18 (100%)
FEV_1/FVC, %	89%	77%	56%	80%	82%
TLC, l	—	4.32 (66%)	4.82 (83%)	—	7.21 (95%)
RV, l	—	0.83 (45%)	2.04 (143%)	—	2.53 (105%)
RV/TLC, %	—	19%	77%	—	35%
DLCO, ml/min/mmHg	—	27.2 (90%)	23.0 (84%)	—	26.0 (86%)
C_{dyn}, %	—	—	—	—	50%[2]
pH	—	7.34	—	—	7.42
$PaCO_2$, mmHg	—	49	—	—	27
PaO_2, mmHg	—	84	—	—	97
HCO_3, mmol/l	—	26	—	—	21

The results correspond to testing done at the time of evaluation, except when indicated for pre-employment results. Percent of predicted is indicated between parentheses. Arterial blood gases were drawn on room air, with the patient resting.
[1]Pre-employment (and pre-exposure) spirometry.
[2]Done in June 1994.

$PaCO_2$ of 39 mmHg, and PaO_2 of 65 mmHg. He was treated with steroids and supplemental oxygen, and was discharged 4 days later, with reportedly normal spirometry and a PaO_2 of 84 mmHg. Following discharge from the hospital, the patient complained of persistent and progressively worsening dyspnea and wheezing on exertion (several blocks or three flights of stairs at the time of evaluation), and atypical chest pain.

The patient had no history of pre-existing pulmonary or allergic disease, and was a lifetime non-smoker. His physical examination was unremarkable. He had a normal chest radiograph, and pulmonary function testing revealed a mild restrictive ventilatory defect with normal diffusion capacity, clearly absent from his pre-employment spirometry (Table I). The flow volume curve was normal, and methacholine bronchoprovocation was negative. The arterial blood gas studies (see Table I) revealed mild respiratory acidosis with normal PaO_2 (unchanged compared with that on discharge from the hospital). He had limited exercise tolerance, but no desaturation was observed with exercise. The clinical picture was considered consistent with a restrictive lung disease, secondary to acute ammonia inhalation injury. The patient was followed by different physicians over the next several years, and he has continued to be symptomatic.

Case 2

Mr. B was a 27-year-old Afro-American man referred for evaluation 26 months after his occupational overexposure. In June 1987 the patient had been exposed to anhydrous ammonia fumes that leaked from a refrigeration system at an ice-making plant. A drain plug was accidentally removed by other workers in a poorly ventilated room. Those workers left the area immediately, but the patient was unaware of the leak until he noted a very strong odor. It then took him approximately 1½–2 min to leave the room where the leak had occurred. Outside, he noted considerable difficulty breathing; irritation of his eyes, nose, and throat; and burning of his skin. He was admitted to a local hospital in respiratory failure. The (preintubation) arterial blood gas on 15 l/min of oxygen showed a pH of 7.54, $PaCO_2$ of 22 mmHg, and PaO_2 of 65 mmHg. He was mechanically ventilated for approximately 24 hr, and after extubation he had persistent hypoxemia. He had considerable sputum production but was not treated with antibiotics. He was given intravenous steroids briefly and was discharged after 6 days in the hospital on inhaled bronchodilators. He was followed as an outpatient because of persistent dyspnea on exertion, productive cough, and wheezing.

The patient had smoked half a pack of cigarettes/day for 7 years until the time of the exposure but had no history of pre-existing lung disease. On physical examination in 1989, there were expiratory wheezes; forced expiration was slightly prolonged and the chest was resonant to percussion. Pulmonary function testing (see Table I) showed a severe obstructive impairment without response to bronchodilator, increased residual volume, and a normal diffusion capacity. These results were similar to those recorded previously elsewhere, indicating a fixed defect. The chest radiograph was normal, and exercise testing could not be performed because of marked dyspnea with minimal effort. The clinical picture of this patient was consistent with a diagnosis of

chronic obstructive pulmonary disease, but (constrictive) bronchiolitis obliterans cannot be excluded.

Case 3

Mr. C was a 46-year-old Caucasian former truck driver who was evaluated in March 1994. In January 1992 he was unloading a tank containing ammonium hydroxide (NH_4OH) solution (29.4% concentration of NH_3) at a paper mill. He was sprayed with that solution and exposed to ammonia fumes. He was admitted to a local hospital, where chemical mucocutaneous burns were treated. During his 5-day hospitalization, he complained of dyspnea and productive cough, presented with wheezing, and was treated with nebulized bronchodilators. The chest radiograph showed minimal areas of atelectasis. Since his discharge from the hospital (for 2 years before his visit to us), the patient had been complaining of persistent dyspnea at rest and on exertion, with frequent acute episodes of dry cough, wheezing, increased dyspnea, and paresthesias in his hands and feet.

The patient's medical history was only relevant for very mild obstructive sleep apnea, diagnosed in March 1988 and treated with uvulo-palato-pharyngoplasty in March 1989 with complete resolution. Except for malaria in 1965, he had otherwise been very healthy and capable of considerable physical effort at work. He had been treated with oral and inhaled bronchodilators, with very limited symptomatic improvement. He had smoked an average of 1–1½ packs of cigarettes per day for 17 years but had quit 12 years before his visit (at age 34).

The results of the pulmonary function tests and room-air arterial blood gases are summarized in Table I (including pre-employment spirometry). The arterial blood gases showed mild chronic respiratory alkalosis with normal PaO_2. There was no evidence of ventilatory limitation by exercise testing, but the test was terminated early because of complaints of dyspnea and hyperventilation. His chest radiographs had been reported as normal, and a high-resolution chest computed tomography (CT) scan (from March 1994) showed only some areas of basilar atelectasis. A methacholine bronchoprovocation test was positive. The static compliance decreased by 50% at a respiratory rate of 32/min, indicating frequency dependence [Woolcock et al., 1969]. The acute episode was consistent with a diagnosis of chemical laryngotracheobronchitis and possibly pneumonitis. With regard to the chronic symptoms, there was evidence of nonspecific bronchial hyper-reactivity and small airways disease. The patient also had a hyperventilation syndrome [George et al., 1990], in all likelihood related to a post-traumatic stress disorder following this occupational overexposure, and which partially explained his symptom of dyspnea.

DISCUSSION

Inhalation of hydrosoluble irritants (like ammonia) is typically associated with proximal airway injury, and relative sparing of the more distal small airways and the alveoli. However, factors that increase the effective exposure dose (e.g., exposure to very high concentrations, or for prolonged periods of time, increased minute ventilation, adsorption to inhaled particulate matter) can facilitate access to the more distal portions of the lung. Less water-soluble irritants (like phosgene or nitrogen dioxide) affect the proximal airways to a lesser degree but are more likely to injure the pulmonary parenchyma [Rorison and McPherson, 1992; Balmes, 1992]. Ammonia is a highly hydrosoluble gas, extensively used in a wide variety of industrial processes. In solution with water, it forms ammonium hydroxide, which can cause liquefaction necrosis and alkali burns [Close et al., 1980]. As it dissolves, it releases heat and is therefore capable of causing thermal injury [Balmes, 1992].

The acute and chronic conditions that have been reported in association with massive ammonia exposure are listed in Table II. The severity of the acute episode is variable and may be proportional to the effective exposure dose [Close et al., 1980; Caplin, 1941]. There are few pathophysiologically well-characterized chronic pulmonary diseases due to massive exposures to ammonia, and clinical follow-up for at least 1 year is available for only a minority (35 of 94) of the cases reported in the literature [Brille et al., 1957; Lepine and Soucy, 1962; Levy et al., 1964; Sestier et al., 1969; Kass et al., 1972; Walton, 1973; Close et al., 1980; Hoeffler et al., 1982; Flury et al., 1983; Bernstein and Bernstein, 1989]. This is in part due to the acute mortality from the episode: Death occurred instantaneously or in-hospital within 60 days of the episode in 20 (21%) of the 94 reported cases [Slot, 1938; Caplin, 1941; Derobert et al., 1964; Walton, 1973; Sobonya, 1977]. Death usually resulted from severe laryngeal edema and obstruction, non-cardiogenic pulmonary edema, or extensive pneumonic complications.

The association between massive ammonia exposure and bronchiectasis is probably the best documented, varying from 2 months to 2 years after the acute episode [Leduc et al., 1992; Kass et al., 1972; Sobonya, 1977]. The patients have usually had severe clinical disease immediately after the exposure, with chemical tracheobronchitis or pneumonitis (in some cases requiring mechanical ventilation) and variable findings on the chest radiograph. The presence of bacterial superinfection was documented or suspected (and treated with antibiotics) in at least 5 of 7 cases [Leduc et al., 1992; Kass et al., 1972; Flury et al., 1983; Sobonya, 1977], which suggests that this may be a necessary predisposing factor for the future development of bronchiectasis. However, in one case report [Sestier et al., 1969] there was no mention of bacterial infection, and the possibility of chem-

TABLE II. Pulmonary Conditions Associated With Ammonia Inhalation Injury

Conditions	References
Acute	
Pulmonary edema	Close et al. [1980], Sobonya [1977], Derobert et al. [1964]
Laryngitis/tracheobronchitis (with or without obstruction)	Leduc et al. [1992], Close et al. [1980]
Bronchiolitis	Walton [1973], Sobonya [1977]
Bronchopneumonia	Flury et al. [1983], Sobonya [1977], Derobert et al. [1964]
Chronic	
Bronchiectasis	Leduc et al. [1992], Kass et al. [1972], Close et al. [1980]
Bronchospasm/asthma	Bernstein and Bernstein [1989], Flury et al. [1983]
Bronchiolitis	Kass et al. [1972], Walton [1973], Sobonya [1977]
COPD	Brille et al. [1957], Lépine and Soucy [1962]

COPD = chronic obstructive pulmonary disorder.

ical injury and edema to the peripheral airways with progressive dilatation of the more proximal ones could be thus suggested.

The association of chronic bronchospasm and asthma with ammonia inhalation injury has also been reported [Bernstein and Bernstein, 1989; Flury et al., 1983]. The terms *reactive airways dysfunction syndrome* (RADS) and *irritant-induced asthma* have been applied to the resulting condition and are currently considered equivalent [Bernstein and Bernstein, 1989; Brooks and Bernstein, 1993]. Long-term persistence and possibly irreversibility have been described. The de novo development of asthma symptoms and airway hyperreactivity would be necessary to make a diagnosis of occupational asthma, but in practice this is difficult or impossible to document in most cases.

Chronic obstructive pulmonary disease (COPD) as a long-term sequela of ammonia inhalation injury has been less well documented, since no histopathology (except for endobronchial biopsies) has been presented. No information about smoking was provided, but the patients were relatively young (37, 40, and 54 years old), and functional studies revealed an obstructive ventilatory defect with air trapping [Brille et al., 1957; Lepine and Soucy, 1962]. To our knowledge, our case no. 2 has been the youngest patient (27 years old) in whom COPD manifested and was diagnosed after massive ammonia inhalation, which could not be attributed to his relatively mild smoking habit or to an inherited antiprotease deficiency.

Bronchiolitis obliterans was an associated histopathologic finding in at least two reports of ammonia exposure at autopsy. Pulmonary edema with hemorrhage [Walton, 1973] and bronchopneumonia and bronchiectasis [Sobonya, 1977] were the predominant features. In both cases the exposure was massive, and survival did not exceed 2 months [Sobonya, 1977]. Some cases of (constrictive) bronchiolitis obliterans may be clinically indistinguishable from COPD, but the prognosis is usually poorer. This condition is believed to result from injury to the small airways, which include the noncartilaginous bronchioles of less than 2 mm in internal diameter, from approximately the 8th through the 20th generation of the bronchial tree. The small airways constitute the site of up to 40% of the normal airway resistance and are probably the primary target of different toxins (including cigarette smoke) that cause chronic lung disease [Kennedy et al., 1985; Brille et al., 1957; Wright, 1985]. Pulmonary function testing (including midexpiratory flow measurements such as FEF_{25-75}) is unreliable to detect abnormalities of the small airways [Kennedy et al., 1985; Wright et al., 1984], and several tests have been proposed for this purpose, including density dependence of flow (breathing air and helium), nitrogen washout [Wright, 1989], and frequency dependence of compliance test [Woolcock et al., 1969]. The use of the latter has been recommended to evaluate at the experimental level the effects on lung function of inhaled toxicants [Mauderly, 1991]. A decrease of 20% or more in lung compliance at high respiratory rates (60–80/min) is considered abnormal [Woolcock et al., 1969]. Clinical uses in the setting of inhalation injuries have very rarely been reported [Fleming et al., 1979; Kass et al., 1972].

Inhalation injury has been infrequently associated with chronic interstitial lung disease, with restrictive ventilatory pattern with or without decreased diffusion capacity [Balmes, 1992]. Ammonia would be expected to cause this complication very rarely, due to the previously discussed predominant pattern of involvement of the more proximal airways. Our case no. 1 had a purely restrictive pattern, with normal diffusion capacity and chest radiograph, and no oxygen desaturation on exercise. The change in lung function was clearly demonstrated in this young man (compared with pre-exposure spirometry), and no other potential cause for the abnormality was found. However, definitive (open lung

biopsy) or additional supporting diagnostic procedures (e.g., chest CT scanning) were not performed.

Many of the reports to date have not presented physiological data similar to this patient. In the two cases of ammonia inhalation injury in which a restrictive dysfunction was ever mentioned, no histopathologic documentation was available, probably because there was no clinical indication for a biopsy procedure (as in our case). In one case, the restrictive pattern was present only acutely and mixed with features of obstruction [Vialard, 1951]. In the other [Flury et al., 1983], airways obstruction was clearly predominant, but the authors also reported persistently decreased elastic recoil and static compliance.

In order to improve the diagnosis and potentially the treatment of patients with chronic symptoms and physiological alterations due to irritant exposure, it is advisable to carefully and sequentially evaluate each level of the respiratory tract by radiological and physiological testing. If the routine pulmonary function tests (spirometry, lung volumes, and diffusion capacity) and chest radiograph fail to characterize the pathologic process underlying a patient's symptoms, consideration should be given to high-resolution CT chest imaging (HRCT), nonspecific bronchoprovocation with methacholine, pulmonary exercise test, and small airways tests. These (now more standard) tests could be ordered sequentially as clinically indicated, based on the already discussed chronic conditions associated with this type of injuries. HRCT is quite useful to detect and characterize interstitial lung disease [Zwirevich and Muller, 1992], as well as bronchiectasis [Naidich et al., 1982]. Nonspecific bronchoprovocation testing is very sensitive to detect airways hyper-reactivity, although its specificity is limited.

Whether the specialized tests of small airway disease mentioned earlier reflect more inhomogeneity of elastic properties of the lung than bronchiolar disease per se remains controversial [Wright, 1989]. In either case, they reflect an abnormal physiologic finding that may help explain persistent respiratory symptoms in patients with otherwise normal or near-normal routine tests. Pulmonary exercise testing can be helpful in establishing the cause of dyspnea and excluding cardiac disease, and in detecting interstitial lung disease. It may also be helpful in some cases to estimate the degree of functional respiratory impairment, especially when it may be felt to have been underestimated by routine testing [American Thoracic Society, 1986].

Lastly, it is important to emphasize that massive ammonia exposures are also frequently associated with nonpulmonary conditions that can pose significant clinical challenges (as illustrated by case no. 3), both acutely (e.g., mucocutaneous burns) or chronically (e.g., post-traumatic stress disorder) [Schottenfeld, 1994]. Adequate and intensive treatment is indicated in order to prevent additional sources of chronic disability [Slot, 1938; Levy et al., 1964].

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