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Occupational causes of constrictive bronchiolitis

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Abstract

Purpose of review—New literature from 2009 to 2012 regarding occupational constrictive bronchiolitis challenges textbook descriptions of this disease, formerly thought to be limited to fixed airflow limitation arising in the wake of accidental overexposure to noxious chemicals. Indolent evolution of dyspnea without a recognized hazardous exposure is a more common presentation.

Recent findings—Biopsy-confirmed case series of constrictive bronchiolitis from US soldiers, Iranian survivors of sulfur mustard gassing, hospital-based studies, and flavoring-related cases document that indolent constrictive bronchiolitis cases can have normal spirometry or either restrictive or obstructive abnormalities. High-resolution computerized tomography studies can be normal or reflect air-trapping and mosaic attenuation on expiratory films. Thus, in the absence of noninvasive abnormalities, the diagnosis in dyspneic patients may require thoracoscopic biopsy in settings in which exposure risk has not been recognized. Many workers with occupational constrictive bronchiolitis stabilize with cessation of exposures causing bronchiolar epithelial necrosis.

Summary—Clinicians need a high index of suspicion for constrictive bronchiolitis in young patients with rapidly progressing exertional dyspnea, regardless of spirometric and radiologic findings. Identification of novel causes and exposure-response relations for known causes are needed to provide guidance for protecting workers at risk for this largely irreversible lung disease.

Keywords

bronchiolitis obliterans; constrictive bronchiolitis; diacetyl; flavorings; sulfur mustard

INTRODUCTION

A major reconceptualization of occupational constrictive bronchiolitis is underway, supported by evidence from pathologic case series and population-based studies of those exposed to occupational and environmental toxins. This review covers the evolution of this thinking from publications dating from 2009 through late 2012. The focus is on constrictive bronchiolitis and excludes bronchiolitis obliterans and organizing pneumonia, although

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Conflicts of interest

The author has no financial relationship with a commercial entity that has an interest in the subject of this manuscript.

overlap syndromes exist from common exposure. The old literature is confusing because nomenclature has evolved, with bronchiolitis obliterans having been used historically to designate both constrictive and proliferative bronchiolitides. This review does not address organ transplant-associated bronchiolitis obliterans syndrome (BOS).

MAJOR FINDINGS

The reconceptualization of constrictive bronchiolitis from the understanding of the twentieth century includes the following observations: the major disease burden is the indolent evolution of constrictive bronchiolitis in persons with no history of acute presentation with pulmonary edema from an overwhelming exposure. The spectrum of spirometric abnormalities in biopsy-confirmed cases includes normal, restrictive, obstructive, and mixed restrictive and obstructive physiologies. The radiologic tools for clinical diagnosis of bronchiolar diseases are insensitive. Exposure-response information is absent for exposures causing both acute and indolent forms of constrictive bronchiolitis. These points are supported by recent literature concerning flavoring-related lung disease in worker populations; biopsy-confirmed constrictive bronchiolitis in US soldiers returning from Iraq and Afghanistan; follow-up of Iranians gassed with sulfur mustard in the 1984–1988 Iraq–Iran war; and newly documented causes of and industries with occupational constrictive bronchiolitis.

Indolent evolution of constrictive bronchiolitis

In 2002, diacetyl-related ‘popcorn lung’ disease became the paradigm for indolent evolution of constrictive bronchiolitis, although it was by no means the first recognition of this phenomenon. Even in industries manufacturing flavorings, cases had occurred for more than 15 years. However, attribution of such cases to specific chemicals or to occupation was delayed because the absence of acute presentation pointed to no dangerous overexposure. In contrast, most of the literature on constrictive bronchiolitis in the twentieth century concerned case reports that were attributable to occupational exposure because healthy workers had toxic exposures, pulmonary edema in close sequence, recovery, and evolution of fixed airways obstruction consistent with constrictive bronchiolitis in the weeks following their acute presentation. The few compilations of cases of ‘silo-fillers lung’ documented that some cases had not consulted medical attention for an acute presentation [1,2], compatible with an insidious evolution of constrictive bronchiolitis even after a single toxic exposure to oxides of nitrogen.

In contrast, flavoring-related constrictive bronchiolitis often developed insidiously early in employment as a response to usual exposures to diacetyl and perhaps other flavoring chemicals in the microwave popcorn, flavoring manufacturing, and diacetyl manufacturing industries. Because flavorings are regarded as safe for ingestion by the Food and Drug Administration, their inhalation hazard for workers was not anticipated. Without clusters of cases of a rare disease prompting epidemiologic investigation, new causes of constrictive bronchiolitis are unlikely to be recognized, as they usually do not have symptoms exacerbated by a work-related exposure that might be a clue regarding cause.

A cluster of cases in US military personnel serving in Iraq and Afghanistan was documented by thoracoscopic biopsies on soldiers who could no longer meet service requirements for physical performance [3▪▪]. Of 38 with constrictive bronchiolitis, 28 reported having been exposed to effluents of a sulfur mine fire in 2003 that produced high ambient air levels of sulfur dioxide, a known cause of constrictive bronchiolitis. Others suspected effluents from open burn pits in which plastics, batteries, Styrofoam, and usual wastes were ignited with jet fuel at many military bases. These cases were insidious in symptom development, obscuring causal exposures, and precipitated extensive controversy in military and Veterans Administration personnel, in part because of twentieth century understanding of constrictive bronchiolitis [4▪,5▪▪, 6▪,7▪,8▪▪].

A third example of newly recognized constrictive bronchiolitis is the 50 000 Iranians followed for more than 20 years after sulfur mustard gassing in the Iraq–Iran war [9]. Respiratory complaints developed in many without a history of acute respiratory compromise. Although the spectrum of diseases was initially described as asthma, chronic bronchitis, bronchiectasis, large airway stricture, and pulmonary fibrosis, the underlying basis for the respiratory sequelae is constrictive bronchiolitis [10▪▪]. As in the military case series above, this rediagnosis was based on evaluation of thoracoscopic biopsies of 15 cases evaluated by an international pathology panel [11] following the report of a Kurd with constrictive bronchiolitis being evaluated for lung transplant many years after sulfur mustard gassing [12]. The Iranian cohorts are a valuable source of population-based data on constrictive bronchiolitis [13▪▪].

One of the major observations from the flavoring work is that indolently evolving constrictive bronchiolitis does not have the relentless downhill course that is characteristic of BOS posttransplant and collagen vascular constrictive bronchiolitis. Affected flavoring-exposed workers appear to largely stabilize within a couple of years of exposure cessation. Although this stabilization was demonstrated earlier among the sentinel case patients and workers followed with nearly 3 years of spirometry in the sentinel microwave popcorn plant [14,15], more recent publications substantiate this observation [16▪▪]. This may be the case among some Iranians after a single exposure to sulfur mustard [10▪▪]. Other recent studies confirming this natural history of occupational constrictive bronchiolitis include a case from World Trade Center exposures [17], from iron oxide in copiers [18], along with historical nitrogen oxides cases. Indeed, although constrictive bronchiolitis does not usually respond to corticosteroid treatment, functional improvement has been described recently in selected cases [17,18], as was also described in some historical nitrogen oxides cases.

Spectrum of spirometric abnormalities

A major conceptual advancement in the last 4 years has been that constrictive bronchiolitis is not always accompanied by fixed airways obstruction. Biopsy-confirmed case series show that spirometry can be normal, restrictive, obstructive, or mixed. Earlier reports of such biopsy-confirmed cases [11,19] were largely ignored until the military cases precipitated controversy regarding the appropriateness of biopsy in persons with normal physiology [3▪▪]. Of the 38 service members with constrictive bronchiolitis, 32 had normal spirometry, three had restrictive, two had obstructive, and one had mixed spirometric abnormalities. Similarly,

among 15 biopsied mustard gas cases (half with constrictive bronchiolitis), Ghanei *et al.* [11] showed that 13 had normal spirometry, one had restrictive, and one had obstructive abnormalities. Markopoulou *et al.* [19], in a sequential series of biopsy-confirmed cases, reported that four had normal spirometry, 11 had obstruction, one had restriction, one had a mixed pattern, and four had isolated air trapping. Figueiredo's *et al.* [18] case also had normal physiologic indices. There is also evidence that spirometric abnormalities are not always fixed in response to bronchodilators [10▪▪,17,19].

The recognition of this spectrum of abnormalities in biopsy-confirmed cases precipitated a resynthesis of flavoring-related cross-sectional studies in which restrictive abnormalities had been largely ignored, although present in nearly every workforce screened with spirometry [20▪▪]. The prevalence of exertional shortness of breath or trouble with breathing was of course much greater in flavoring-exposed workers than the prevalence of spirometric abnormalities, as has been shown in diacetyl manufacturing workers as well [21]. The production workforce of one flavoring manufacturing plant had a 28% prevalence of spirometric restriction and only 3.7% with any obstruction [22▪]. Serial spirometry in these workers documented that those with higher potential for flavoring exposures had a seven-fold prevalence of excessive declines in forced expiratory volume in one second (FEV1) than workers with lower potential for flavoring exposures, suggesting an occupational cause. Many of the workers with excessive FEV1 declines still had spirometric measures that were within the normal range and would not be identified with cross-sectional spirometric screening.

Several studies address advances in longitudinal spirometric surveillance pertinent to identifying workers at risk of an irreversible constrictive bronchiolitis before they sustain impairment. Approaches using longitudinal limits of decline in FEV1 are superior to relative percentage decline among flavoring-exposed workers [23]. National Institute for Occupational Safety and Health (NIOSH) freeware to address longitudinal FEV1 decline, adjusting for intraindividual variation as a quality measure, is now available [24▪▪,25▪]. The American College of Occupational and Environmental Medicine guidance statement recommends medical referral for workers at risk for an endpoint disease, such as bronchiolitis obliterans in flavoring workers, with declines of 10–15% in FEV1, after allowing for expected loss due to aging [26]. Evaluation of longitudinal decline in serial spirometry data for flavoring manufacturing workers in industry-wide surveillance showed that the occupational risk factors for excessive FEV1 decline overlapped with the risk factors for obstructive spirometry in cross-sectional evaluation, although nearly all those with excessive decline had normal spirometry [27▪,28▪▪].

Insensitivity of noninvasive diagnostic tools

Just as spirometric abnormalities are insensitive for biopsy-confirmed constrictive bronchiolitis, these case series show that even high-resolution computerized tomography (HRCT) scans are insensitive. When abnormal, HRCT scans show air-trapping and mosaic attenuation on expiratory images. However, King *et al.* [3▪▪] described 25 of 37 HRCTs to be normal in US service members with constrictive bronchiolitis, and only six had air-trapping. Similarly, Ghanei *et al.* [11] showed that biopsy-confirmed cases did not all have

HRCT abnormalities, but reported that HRCT could help differentiate among resistant asthma, sulfur mustard-related constrictive bronchiolitis, and smoking-related injury [29].

Representatives of military medicine have argued that surgical diagnostic studies are not warranted in dyspneic service persons without abnormal test results [30], but this position guarantees that the extent of service-related constrictive bronchiolitis will remain undescribed. Although a pathologic diagnosis will not lead to therapy for constrictive bronchiolitis at present, apart from restriction from further exposure to suspected causes, future efforts at prevention of such disease are hampered by the lack of understanding of extent and causes of disease in war theatres. As the pathologic diagnosis is difficult to make and sometimes missed due to the patchy nature of disease, need for serial sections, and special stains, case patients that come from a workforce with sentinel cases may not require thoracoscopic biopsy to confirm the probable diagnosis, as constrictive bronchiolitis is a rare disease in the general population. However, patients with dyspnea with normal physiology and radiologic findings are unlikely to be diagnosed without biopsy.

Exposure-response relations and challenges

Historically, little information has been available about exposure levels resulting in constrictive bronchiolitis because accidental overexposures are never anticipated. The same is true for emerging causes of indolent constrictive bronchiolitis. Measurements are not available in industry in the absence of hazard recognition or regulation. In the microwave popcorn industry, substantial efforts have been made to reconstruct historical exposures to diacetyl, despite the absence of personal exposure measurements before interventions were begun and despite a flawed measurement technique that was affected by absolute humidity, temperature, and days to extraction in the analytic laboratory [16▪▪,31▪▪]. The exposure reconstruction is the basis of quantitative risk assessment to support a recommended standard for occupational exposures to diacetyl and 2,3-pentanedione, a structurally similar α-diketone with similar hazard that is used as a substitute for diacetyl by flavoring manufacturers [31▪▪,32,33▪–35▪]. NIOSH recommends standards for public comment of 5 parts per billion (ppb) for diacetyl and 9.3 ppb for 2,3-pentanedione, the latter limited by available measurement sensitivity despite its having comparable toxicity to diacetyl [31▪▪].

Other publications have taken different approaches to protective standards. Maier *et al.* [36] used animal toxicity data to propose a standard of 200 ppb. Since then, more robust animal data have become available and likely will be incorporated in the NIOSH criteria document revision [33▪,34▪]. Lockey *et al.* [37] found that microwave popcorn workers with at least 800 ppb-years of cumulative exposure had excessive decline in FEV1 over a 1-year period and a 9.2-fold risk of airway obstruction. Egilman *et al.* [38] proposed a standard of 1 ppb on the basis of the available epidemiologic and animal data. They reported three cases of biopsy-confirmed bronchiolitis obliterans in consumers of microwave popcorn [39], but attribution to butter flavorings is difficult in individual cases. The Flavor and Extract Manufacturers Association of the United States updated their 2004 publication on priority chemicals with potential respiratory hazards, adding 2,3-pentanedione [40].

Newly recognized settings of risk for occupational constrictive bronchiolitis

In the last 4 years, case reports have documented risk of constrictive bronchiolitis in additional industries with flavorings exposure, such as cookie manufacture [41▪] and the coffee industry (Huff S, unpublished data). Surveillance and serial follow-up studies [16▪▪, 20▪▪,27▪,28▪▪,31▪▪,32,37] in microwave popcorn and flavoring industries have contributed to our understanding of occupational lung disease risk with flavorings exposure. Ongoing NIOSH investigations are likely to be published regarding additional flavoring manufacturing facilities, mortality follow-up in the sentinel Missouri microwave popcorn worker cohort [42], a coffee flavoring and roasting plant, and a pet food manufacturing facility. Lockey *et al.* are analyzing a 6-year longitudinal study of a four-plant cohort in the microwave popcorn industry.

Case reports of new or old exposure associations include hydrogen sulfide in a Persian Gulf oil refinery [43], ammonia [44], household cleaners [44], iron oxide from copy machines [18], uncharacterized military exposures in Iraq and Afghanistan [3▪▪], and styrene or other exposures in fiberglass boat building [45▪▪]. Iranian investigators are reporting many mechanistic associations and clinical characteristics of those followed for 20 years after sulfur mustard gassings [10▪▪]. In addition, reviews of sulfur mustard toxicology summarize some of the historical clinical data, but often are uncritical of earlier publications before the recognition of constrictive bronchiolitis as the major sequel of remote injury [13▪▪,46▪▪,47]. Finally, the common denominator of respiratory epithelial necrosis with damage below the basement membrane from gases and vapors associated with constrictive bronchiolitis will likely result in future reinterpretation of earlier cases that may have been attributed to other disease outcomes after inhalation of acids, halogens, and many other chemicals. Since nearly all causes of constrictive bronchiolitis are gases, the relevance of particulate exposures to constrictive bronchiolitis, independent of adsorbed chemicals recognized to cause epithelial injury, remains to be determined [17,48,49].

CONCLUSION

Cases of indolent constrictive bronchiolitis without recognized overexposures can prompt identification of new causes through referral to public health authorities for epidemiologic follow-up of sentinel case-patients' coworkers and workplace exposures, as has occurred in flavoring-exposed workforces. The index of suspicion for this diagnosis should be high in persons with unexplained exertional dyspnea because the pathologic disease can exist with normal, restrictive, or obstructive spirometry tests and normal HRCT. With insensitive non-invasive diagnostic tests for bronchiolar disease, the diagnosis of constrictive bronchiolitis may require thoracoscopic biopsy. Young workers with rapid development of exertional dyspnea unresponsive to bronchodilator or corticosteroid treatment merit consideration of a constrictive bronchiolitis diagnosis, even if they have no evidence of air-trapping or spirometry abnormalities. As exposure-response data are largely lacking, additional research is needed on epidemiology, risk assessment, and animal toxicology for suspected causes of this underrecognized disease, particularly when it arises in an indolent form without acute pulmonary reactions that trigger recognition of hazardous levels of exposure. Recognition of

new causes can lead to primary and secondary prevention for workers, who often stabilize with cessation of the causative exposure.

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KEY POINTS

- Indolent constrictive bronchiolitis often remains undiagnosed because no acute presentation points to a cause of lung injury.
- Both physiologic and radiographic studies are insensitive for biopsy-confirmed constrictive bronchiolitis.
- A high index of suspicion for constrictive bronchiolitis is prudent in evaluating young dyspneic patients with complaints out of proportion to spirometric measures of impairment.
- Report of sentinel cases of constrictive bronchiolitis can motivate public health follow-up of coworkers and others with similar industrial exposures.
- Indolent constrictive bronchiolitis likely affects many more workers than those with acute presentation with pulmonary edema after an overexposure to noxious gases or vapors.