CLINICAL PROBLEM-SOLVING

Caren G. Solomon, M.D., M.P.H., *Editor*

A Burning Question

Alexander S. Rabin, M.D., Caroline W. Davis, M.D., Anays M. Sotolongo, M.D., Michael J. Falvo, Ph.D., and John J. Osterholzer, M.D.

In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader (regular type). The authors' commentary follows.*

From the Division of Pulmonary and Critical Care, Department of Medicine, Veterans Affairs Ann Arbor Healthcare System, and the Division of Pulmonary and Critical Care, Department of Medicine, University of Michigan — both in Ann Arbor (A.S.R., C.W.D., J.J.O.); and the Airborne Hazards and Burn Pits Center of Excellence, War Related Illness and Injury Study Center, Veterans Affairs New Jersey Healthcare System, East Orange (A.M.S., M.J.F.), and the Division of Pulmonary and Critical Care, Department of Medicine (A.M.S.), and the Departments of Pharmacology, Physiology and Neuroscience, and Physical Medicine and Rehabilitation (M.J.F.), Rutgers New Jersey Medical School, Newark. Dr. Rabin can be contacted at alexander.rabin@va.gov or at the Veterans Affairs Ann Arbor Healthcare System, 2215 Fuller Rd., Ann Arbor, MI 48105.

N Engl J Med 2022;386:1352-7.
DOI: 10.1056/NEJMcps2119930

A 35-year-old man presented to a Veterans Affairs (VA) pulmonary clinic with dyspnea and cough. The patient's symptoms began 4 years before presentation and had progressed over time. Two years before presentation, he had attempted to enroll in a police academy but was unable to complete the required physical training regimen. He reported shortness of breath, cough, and burning retrosternal chest pain that occurred with any degree of exertion but was most pronounced while he was running. He noted that these symptoms never occurred at rest. He reported that he was embarrassed about his inability to exercise and asked why he could no longer keep up with his peers. He was previously evaluated for these symptoms at another clinic, where he had been told he might have asthma. He received a prescription for inhaled albuterol for use before exercise, but his cough and shortness of breath continued to worsen despite this treatment.

Dyspnea, cough, or wheezing with evidence of variable airflow obstruction must be present to make a diagnosis of asthma. In patients with exercise-induced bronchoconstriction, these symptoms typically occur after exertion. The lack of clinical improvement with albuterol and the slow progression of the patient's symptoms lower the probability of asthma. Although the combination of dyspnea and cough suggests a respiratory origin, other causes of dyspnea should be considered, including cardiovascular disease, anemia, neuromuscular weakness, and physical deconditioning.

The patient had gastroesophageal reflux disease, chronic rhinitis, obstructive sleep apnea, post-traumatic stress disorder, and obesity. He had gained 13 kg (28 lb) since the onset of symptoms 4 years earlier. He had no childhood history of asthma or seasonal allergies. He was adherent to nightly treatment with continuous positive airway pressure. His medications included inhaled albuterol, fluticasone nasal spray, and pantoprazole. He had no known drug allergies.

Gastroesophageal reflux disease, rhinitis, and asthma are the three most common contributors to chronic cough, yet treatment of these conditions in this patient has not resulted in alleviation of cough. Although post-traumatic stress disorder should be considered when evaluating patients who have dyspnea and chest discomfort, the association of these symptoms with exertion in the absence of any emotional triggers does not support a psychogenic cause in this patient. The relationship of the symptoms to his weight gain should be further explored.

There was no family history of heart or lung disease. The patient had quit smoking 3 years earlier, after having smoked one pack of cigarettes per day beginning at 16 years

of age. He used cannabidiol oil several times per month but did not smoke marijuana. He reported a single episode of vaping 3 years earlier. The patient was currently abstinent from alcohol, although he had a history of excessive alcohol consumption. He lived in Michigan with his wife and two children. He was a U.S. Marine Corps veteran. After discharge from the military, he worked as a janitor and automobile mechanic before taking a medical leave of absence.

Although the patient has no family history of lung disease and only a modest smoking history, early-onset chronic obstructive pulmonary disease due to alpha$_1$-antitrypsin deficiency should be considered, given his young age. Vaping has been linked to acute lung injury, but his symptoms preceded the vaping exposure. Work-exacerbated asthma typically worsens when a person is at work and abates during holidays; the persistence of the patient's symptoms months after taking a medical leave of absence does not support this condition. Conversely, cleaning products can trigger irritant-induced asthma, a type of nonallergic airway hyperresponsiveness that may linger for months after a noxious exposure. The use of a journal kept by the patient to document episodes of dyspnea and to record peak flow values may clarify the pattern of illness.

The patient appeared well and had no observable dyspnea at rest. The temperature was 36.5°C, the pulse 82 beats per minute, the blood pressure 132/75 mm Hg, the respiratory rate 18 breaths per minute, and the oxygen saturation 97% while the patient was breathing ambient air. The weight was 104 kg (230 lb), the height 178 cm (70 in), and the body-mass index (the weight in kilograms divided by the square of the height in meters) 33. There was mild erythema of the nasal mucosa. The trachea was midline, and breath sounds were normal in both lungs, with no stridor, wheezes, or rales. Diaphragmatic excursion was normal on percussion. Heart sounds were regular with no murmurs. There was no peripheral edema. The muscle strength was 5/5 in the arms and legs. The remainder of the examination was normal.

The patient's white-cell count was 7590 per cubic millimeter, with 62.2% neutrophils, 28.1% lymphocytes, 6.3% monocytes, 0.7% basophils, and 2.2% eosinophils (absolute eosinophil count, 170 per cubic millimeter). The hematocrit was 47.3%, and the platelet count 242,000 per cubic millimeter. The IgE level was 27 IU per milliliter (reference range, 6 to 495). An electrocardiogram was normal.

Obesity may lead to deconditioning and dyspnea; however, it would not explain the patient's persistent cough. There is no indication of a neuromuscular disorder or diaphragmatic weakness. The remainder of the examination is normal, although a physical examination has low sensitivity for the detection of airway disease. Laboratory testing does not indicate evidence of anemia or an allergic phenotype.

Pulmonary-function testing showed adequate effort with narrowed inspiratory and expiratory flow-volume loops but no evidence of a concave expiratory contour that could indicate small-airway obstruction. The forced expiratory volume in 1 second (FEV_1) was 2.63 liters (60% of the predicted value), and the forced vital capacity (FVC) was 3.31 liters (61% of the predicted value); the ratio of FEV_1 to FVC was 0.8. No clinically significant improvement in FEV_1 or FVC was observed after the use of a bronchodilator. The total lung capacity was 4.37 liters (63% of the predicted value), with a residual volume of 1.15 liters (66% of the predicted value) and an expiratory reserve volume of 0.89 liters (47% of the predicted value). The diffusing capacity of the lung for carbon monoxide could not be measured owing to cough. A methacholine challenge did not induce a 20% decrease in FEV_1 from the baseline value. A chest radiograph was normal.

Although a diagnosis of asthma had been considered, the absence of reversible airflow obstruction and the absence of bronchoconstriction after a methacholine challenge effectively rules out this diagnosis. Instead, testing reveals a restrictive ventilatory defect. Restriction occurs in patients with diseases of the lung parenchyma and of the chest wall. The patient's obesity may be associated with chest-wall restriction, with a resultant decrease in the total lung capacity and expiratory reserve volume. Measurement of the diffusing capacity of the lung for carbon monoxide would have been helpful to assess for loss of the surface area of the pulmonary capillaries, possibly resulting from interstitial lung disease or another parenchymal lung process; however, the patient was

unable to complete the necessary breath-holding maneuver. Given the diagnostic uncertainty, I would perform high-resolution computed tomography (CT) of the chest to assess the lung parenchyma.

High-resolution CT images of the chest obtained after a full inspiration and after a forced expiration showed mild air trapping (Fig. 1). There was no evidence of interstitial lung disease.

Air trapping occurs when gas does not adequately escape the alveolar lung units after a forced expiration. On CT, this phenomenon has the appearance of a mosaic pattern with areas of low attenuation on expiratory images. When air trapping is present in isolation, without other parenchymal findings such as bronchiectasis or fibrosis, it is suggestive of small-airway disease, including asthma, chronic bronchitis, or bronchiolitis. The air trapping seen on this patient's CT despite the normal residual volume and normal ratio of residual volume to total lung capacity on pulmonary-function testing may reflect the insensitivity of pulmonary-function testing to detect abnormalities of the small airways. Additional physiological testing would be helpful to better characterize the patient's exercise limitations.

Additional history was obtained during an evaluation at the VA War Related Illness and Injury Study Center. The patient had been deployed twice during Operation Iraqi Freedom between 2003 and 2005 (13 years before presentation). He had worked in convoy security and as a truck driver. As part of his duties, he had routinely deposited paper, cardboard, electronics, used medical supplies, tires, and discarded food into an open burn pit at the military base. In addition, the patient had helped burn human waste that was contained in 50-gallon drums. The waste had been ignited with jet propellant–8 (a kerosene-based fuel) and then stirred until it was no longer visible. No personal protective equipment had been used. He recalled that exposure to smoke from the burn pit and human waste drums triggered a cough and phlegm production. He separately reported exposure to sandstorms and to diesel engine exhaust.

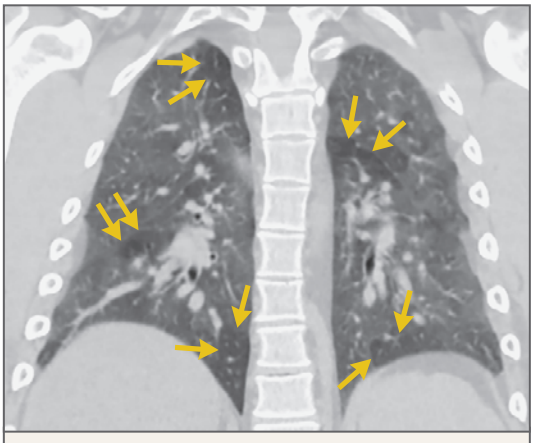

Figure 1. CT of the Chest.
A CT image of the chest obtained at end expiration shows a mosaic attenuation pattern, with areas of lower density (arrows) as compared with the surrounding lung parenchyma, findings that are compatible with air trapping.

It is important to recognize military service as an occupation and to inquire about potential exposures unique to active and former military personnel. The patient was exposed to several respiratory hazards that were not uncommon during deployments to Iraq and Afghanistan in the post–September 11 era. These include sand and dust storms, burn-pit fumes generated from the incineration of trash and human waste, sulfur dioxide emitted from a fire in a sulfur mine, and motor vehicle exhaust.

Tests for antinuclear antibodies, rheumatoid factor, anti–cyclic citrullinated peptide antibodies, and alpha$_1$-antitrypsin deficiency were negative. Repeat pulmonary-function testing continued to show a restrictive ventilatory defect. The diffusing capacity of the lung for carbon monoxide, which had not been measured previously owing to the patient's cough, indicated a mild impairment in gas exchange (63% of the predicted value). The results of the forced oscillation technique (a noninvasive measure of the mechanical properties of the respiratory system) indicated elevated resistance without frequency dependence (a finding suggestive of decreased airway caliber) and reduced reactance (a finding suggestive of decreased lung compliance).

The patient performed maximal cardiopulmonary exercise testing (with the use of a modified Bruce protocol), but the test was terminated after 4 minutes owing to very severe dyspnea, which the patient rated at 9 on a scale of 0 to 10. At the time of test termination, the peak oxygen consumption was 33% of the predicted value and the patient

had exerted 3.6 metabolic equivalents (predicted value, 8.3). The peak heart rate was 123 beats per minute (67% of the predicted value), with no changes on electrocardiography. There was inefficient ventilation, as evidenced by a ratio of minute ventilation to carbon dioxide production of greater than 50 (reference value, <30), as well as a reduced ventilatory reserve, with a ratio of minute ventilation to maximum voluntary ventilation of 0.67 (reference value, >0.8). There was no clinically significant change in the FEV_1 after exercise and no marked decrease in the oxygen saturation.

The findings of inefficient ventilation and a reduced ventilatory reserve suggest a respiratory limitation to exercise. However, the respiratory defect is probably not caused by asthma, given that the FEV_1 did not decrease after exercise. The defect may be localized to the terminal bronchiole; abnormalities in these small airways can be difficult to detect on routine testing. Although the forced oscillation technique is used most frequently in children because it requires minimal effort, its application in this patient further suggests involvement of the small airways.

Obesity and deconditioning could result in a restrictive ventilatory defect, blunted heart rate response, and impaired exercise tolerance. However, the evidence of an underlying small-airway disease should prompt consideration that the small-airway defect precipitated the patient's dyspnea and subsequent weight gain. A range of histopathological abnormalities have been reported in lung-biopsy samples from deployed military personnel with exposures to hazardous substances and near-normal results on physiological testing; these abnormalities include granulomatous pneumonitis, pleural inflammation, and constrictive or other forms of chronic bronchiolitis. A lung biopsy should be considered in this patient to establish a diagnosis of small-airway disease or to identify other potentially treatable conditions.

The patient underwent a video-assisted thoracoscopic lung biopsy. Specimens were obtained from each lobe of the right lung and examined at the Defense Health Agency's Joint Pathology Center. Histopathological analysis identified airway distortion and narrowing, focal segmental obliteration, peribronchiolar metaplasia, and subepithelial thickening due to smooth-muscle hypertrophy and collagen deposition (Fig. 2). There was minimal pigment deposition adjacent to bronchovascular structures, and there was no evidence of emphysema or pleural inflammation. The findings were classified as constrictive bronchiolitis.

Lung-biopsy findings must be interpreted in the context of a patient's exposure history and findings on physiological testing and imaging. Constrictive bronchiolitis, a subtype of small-airway disease, can occur in a variety of clinical contexts. It has been described in patients who have undergone organ transplantation or who have had respiratory infections, in patients with autoimmune disease, and in patients who have had exposure to inhaled toxins such as diacetyl, which

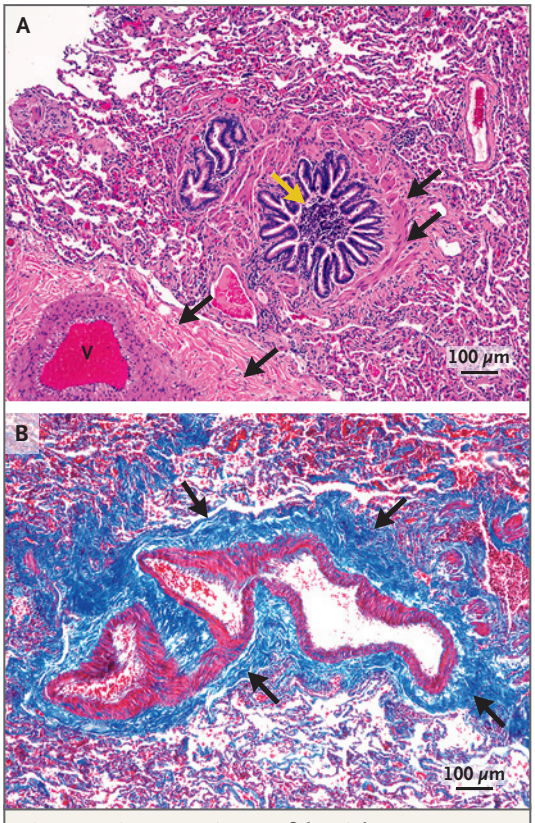

Figure 2. Biopsy Specimens of the Right Lung.
Biopsy specimens of the right lung show features of constrictive bronchiolitis. In Panel A, hematoxylin and eosin staining shows focal segmental luminal obliteration (yellow arrow) and smooth-muscle hypertrophy (black arrows) of the airways and adjacent vasculature (V). In Panel B, trichrome staining shows airway-wall thickening due to subepithelial collagen deposition (blue staining; arrows), which indicates fibrosis of the membranous bronchiole.

is used in food flavoring. In this patient, the history of intense inhalational exposure during military service, imaging findings of air trapping, and histopathological evidence of small-airway injury are consistent with a diagnosis of constrictive bronchiolitis related to deployment.

A multidisciplinary review concluded that the patient had constrictive bronchiolitis and that the temporal relationship of his exposures, symptom onset, and test results provided strong evidence that his condition was attributable to military service. Pulmonary rehabilitation was recommended. He received a prescription for inhaled budesonide and formoterol, and a course of azithromycin three times weekly was initiated. At a clinic visit 2 years later, the patient reported that his cough and dyspnea had abated.

COMMENTARY

Blinding dust storms, black smoke from open burn pits, and plumes of sulfur dioxide are only a few of the respiratory hazards faced by military personnel in the post–September 11 era.[1-3] Care of returning veterans requires recognition of these and other occupational exposures as well as a detailed medical history. In this case, the deployment history in combination with findings that were inconsistent with asthma led to consideration of other causes of small-airway disease.

Diseases of the terminal bronchioles, which are defined as small airways that measure less than 2 mm in diameter and are without cartilage, have long posed a diagnostic challenge.[4,5] Even in the presence of substantive histopathological abnormalities, routine pulmonary-function test results may be normal or may show nonspecific abnormalities. Expiratory CT scans may show air trapping; however, this radiographic finding is subjective and may not be present. For these reasons, the terminal bronchioles are sometimes referred to as the "silent zone" of the lungs. Although efforts are under way to evaluate the usefulness of noninvasive tests such as the forced oscillation technique to better identify small-airway disease in military personnel, they are not yet fully standardized or widely available.[6] At present, surgical lung biopsy may be needed to definitively diagnose diseases of the small airways.

A case series published in the *Journal* in 2011[7] described constrictive bronchiolitis in 38 of 49 soldiers who underwent lung biopsy for unexplained exercise intolerance that had developed after serving in Iraq, Afghanistan, or both. Many of the soldiers reported exposure to a 2003 sulfur-mine fire in Iraq, burn pits, sandstorms, or a combination of these. Of the 38 soldiers with biopsy-proven constrictive bronchiolitis, 34% had entirely normal results on pulmonary-function testing and an additional 50% had an isolated decrease in gas exchange. The high-resolution CT images were normal in 68% of the soldiers; only 16% had radiographic evidence of mild air trapping. Subsequent studies have confirmed histopathological features of constrictive bronchiolitis in formerly deployed military personnel who had unexplained dyspnea. Additional features of granulomatous and chronic pleural inflammation, emphysema, and interstitial fibrosis have also been described.[8-10] The specific agents causing constrictive bronchiolitis in military personnel remain uncertain. The disease has been documented after exposure to other respiratory toxins including diacetyl and sulfur mustard and after exposure to fumes associated with the World Trade Center collapse.[4,11,12]

Approved therapies for constrictive bronchiolitis are lacking, and few data are available regarding treatment.[1,13] Inhaled glucocorticoids and bronchodilators, oral glucocorticoids, long-term treatment with azithromycin, and exercise have all been used to treat the disease on the basis of limited evidence for efficacy in other small-airway diseases such as post-transplantation bronchiolitis and diffuse panbronchiolitis.[4,14]

Several programs have been established to enhance the clinical care of affected persons and to further study the health effects of deployment. The VA Airborne Hazards and Open Burn Pit Registry, which has enrolled more than 298,000 active and former military personnel since its inception in 2014, collects data on potentially hazardous exposures and symptoms with the use of an online questionnaire and allows participants to request a clinical evaluation.[15] More recently, the VA Airborne Hazards and Burn Pits Center of Excellence and the Post-Deployment Cardiopulmonary Evaluation Network were created to better understand and improve the respiratory health of deployed veterans.

This case underscores the importance of ask-

ing about a patient's exposures, including those during military service, and pursuing a more comprehensive evaluation in cases in which initial testing does not yield a diagnosis that adequately accounts for the clinical picture. Although much remains to be learned about the health effects of inhalational exposures during military service, a careful evaluation can help answer our patients' burning questions.

The authors have no potential conflict of interest relevant to this article.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Drs. Darius K. Amjadi and Nabiha Khoury for the histopathological images.

REFERENCES

1. Garshick E, Abraham JH, Baird CP, et al. Respiratory health after military service in Southwest Asia and Afghanistan: an official American Thoracic Society workshop report. Ann Am Thorac Soc 2019;16(8):e1-e16.

2. Krefft SD, Meehan R, Rose CS. Emerging spectrum of deployment-related respiratory diseases. Curr Opin Pulm Med 2015;21:185-92.

3. Smith B, Wong CA, Smith TC, Boyko EJ, Gackstetter GD, Ryan MAK. Newly reported respiratory symptoms and conditions among military personnel deployed to Iraq and Afghanistan: a prospective population-based study. Am J Epidemiol 2009;170:1433-42.

4. Barker AF, Bergeron A, Rom WN, Hertz MI. Obliterative bronchiolitis. N Engl J Med 2014;370:1820-8.

5. Nett RJ, Harvey RR, Cummings KJ. Occupational bronchiolitis: an update. Clin Chest Med 2020;41:661-86.

6. Butzko RP, Sotolongo AM, Helmer DA, et al. Forced oscillation technique in veterans with preserved spirometry and chronic respiratory symptoms. Respir Physiol Neurobiol 2019;260:8-16.

7. King MS, Eisenberg R, Newman JH, et al. Constrictive bronchiolitis in soldiers returning from Iraq and Afghanistan. N Engl J Med 2011;365:222-30.

8. Gutor SS, Richmond BW, Du R-H, et al. Postdeployment respiratory syndrome in soldiers with chronic exertional dyspnea. Am J Surg Pathol 2021;45:1587-96.

9. Krefft SD, Wolff J, Zell-Baran L, et al. Respiratory diseases in post-9/11 military personnel following Southwest Asia deployment. J Occup Environ Med 2020;62:337-43.

10. Gordetsky J, Kim C, Miller RF, Mehrad M. Non-necrotizing granulomatous pneumonitis and chronic pleuritis in soldiers deployed to Southwest Asia. Histopathology 2020;77:453-9.

11. Mann JM, Sha KK, Kline G, Breuer F-U, Miller A. World Trade Center dyspnea: bronchiolitis obliterans with functional improvement: a case report. Am J Ind Med 2005;48:225-9.

12. Ghanei M, Tazelaar HD, Chilosi M, et al. An international collaborative pathologic study of surgical lung biopsies from mustard gas-exposed patients. Respir Med 2008;102:825-30.

13. Respiratory health effects of airborne hazards exposures in the Southwest Asia theater of military operations. Washington, DC: National Academies Press, 2020.

14. Lin X, Lu J, Yang M, Dong BR, Wu HM. Macrolides for diffuse panbronchiolitis. Cochrane Database Syst Rev 2015;1:CD007716.

15. Savitz DA, Styka AN, Butler DA, eds. Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry. Washington, DC: National Academies Press, 2017.