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Case Report

Dendriform pulmonary ossification in military combat veterans: A case series

Jeremy T. Hua [a,b,c,*], Carlyne D. Cool [d], Tami J. Bang [e], Silpa D. Krefft [a,b,c,f], Richard C. Kraus [a], Cecile S. Rose [a,b,c]

[a] Division of Environmental and Occupational Health Sciences, National Jewish Health, Denver, CO, USA
[b] Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado School of Medicine, Aurora, CO, USA
[c] Department of Environmental and Occupational Health, Colorado School of Public Health, Aurora, CO, USA
[d] Department of Pathology, University of Colorado School of Medicine, Aurora, CO, USA
[e] Department of Radiology, National Jewish Health, Denver, CO, USA
[f] Division of Pulmonary and Critical Care Medicine, Veterans Administration Eastern Colorado Health Care System, Aurora, CO, USA

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ABSTRACT

Dendriform pulmonary ossification (DPO) is a rare condition characterized by mature bone formation in the lung. DPO has been linked to various conditions, but little is known about the link between DPO and hazardous airborne exposures. We queried research databases of military personnel evaluated for deployment-related respiratory diseases at two occupational pulmonary medicine clinics (Colorado, USA) for diagnoses of DPO, and summarized demographics, Gulf War military deployment history, medical history, and pulmonary function testing. Chest imaging was independently reviewed and scored by a thoracic radiologist, and all cases had undergone lung tissue biopsy. We identified five male combat veterans with DPO, median age 49 years [range: 32–64]. All had deployed to Southwest Asia or Afghanistan during the First or Second Gulf War, and all reported frequent, intense exposure to diesel exhaust, burn pit emissions, and sandstorms. Lung physiology was abnormal in all cases. The most prevalent chest imaging and histopathology findings were airway-centric injury, inflammation, and retained particulate matter, suggesting substantial hazardous exposure during military deployment. This case series of a rare lung disease from the only two contemporary Colorado clinics serving previously deployed veterans highlights a potential link between airborne hazards and lung injury leading to DPO. A high index of clinical suspicion combined with a detailed occupational history may reveal additional exposure-related associations with DPO. Access to large medical databases of military veterans with linkage to exposure histories may further elucidate risk factors for lung injury with ossification, paving the way for targeted prevention.

1. Introduction

Dendriform pulmonary ossification (DPO) is a rare condition characterized by mature bone formation within the lung parenchyma. Pathophysiologic mechanisms are poorly understood, and DPO can occur without apparent cause or as a secondary response to various pulmonary, cardiac, or other extra-thoracic conditions [1]. DPO has been described in patients with concomitant pulmonary fibrosis,

* Corresponding author. 1400 Jackson St, Denver, CO, 80206, USA.
E-mail address: huaj@njhealth.org (J.T. Hua).

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inflammatory lung disorders, and chronic aspiration [2–4], and diagnosis typically occurs at older ages or on autopsy [2,4–6].

Little is known about potential causative links between DPO and exposure to workplace or environmental hazards. In this case series, we characterize clinical, imaging, and histologic features from five cases of DPO occurring in younger to middle aged combat

Table 1
Demographics, deployment exposures, clinical comorbidities, and diagnostic testing for 5 combat veterans with dendriform pulmonary ossification.

#	Age/ Gender	BMI	Smoking pack-years	Persian Gulf War deployment history[a]	Service branch, job title, and reported exposures	Pulmonary Function Pattern[b]	Chest Imaging Abnormalities	Lung Histology Abnormalities
1	32/M	41	0	18 months: Iraq (2009–10), Afghanistan (2012–13)	Army (MOS 19D – cavalry scout; 92A – logistics specialist): diesel exhaust, burn pits, sandstorms, desert dust, IED blasts, controlled detonations	Restrictive (TLC 72 %)	-DPO (<1/3rd lung involvement), lower-lobe predominant -Moderate bronchial wall thickening -Moderate geographic air-trapping -Branching nodularity	Surgical lung biopsy: -DPO -Bronchiolitis -OP -Chronic pleuritis
2	54/M	31	25	2 months: Iraq (2004)	Air Force (AFSC 1C741 – air control tactics): diesel exhaust, burn pits, sandstorms, IED blasts, desert dust	Restrictive (TLC 75 %)	-DPO (<1/3rd lung involvement), lower-lobe predominant	Transbronchial biopsy: -Chronic inflammation -SMH -Anthracotic pigment
3	49/M	27	0	29 months: United Arab Emirates (1999), Iraq (2003, 2005), Qatar (2009, 2012)	Air Force (AFSC 3E1X1 – HVAC specialist): diesel exhaust, burn pits, oil well fire smoke, sandstorms, desert dust, IED blasts, controlled detonations	Restrictive (TLC 67 %), Diffusion impairment (DLCO 50 %)	-DPO (1/3rd-2/3rd lung involvement), diffuse distribution -Mild lobular air-trapping -Branching nodularity -Emphysema -Pleural thickening	Surgical lung biopsy: -DPO -OP -Emphysema -Anthracotic pigment -Pleural fibrosis Transbronchial biopsy: -Anthracotic pigment
4	46/M	38	0	31 months: Iraq (1990–91, 2003–04, 2005–06), Kuwait (1995)	Army (MOS 13B – cannon crew member/artillery officer): diesel exhaust, burn pits, sandstorms, desert dust, combat dust	Restrictive (TLC 57 %), Diffusion impairment (DLCO 68 %)	-DPO (<1/3rd lung involvement), lower-lobe predominant	Surgical lung biopsy: -DPO -Bronchiolitis -OP -SMH -Anthracotic pigment -Birefringent particulate matter
5	64/M	26	0	45 months: Persian Gulf (1991–98)	Marines (MOS 0801 - artillery officer): diesel exhaust, burn pits, oil well fire smoke, sandstorms, desert dust, combat dust	Air-trapping (RV 140 %)	-DPO (<1/3rd lung involvement), lower-lobe predominant -Mild bronchial wall thickening -Branching nodularity	Surgical lung biopsy: -DPO -Bronchiolitis -OP -Chronic inflammation -SMH -PBM -Emphysema -Granulomas

Table abbreviations: # = Case identification number; AFSC = Air Force Specialty Code; Age = Age at DPO diagnosis; BMI = body mass index (kg/m^2); DLCO = diffusion capacity of the lungs for carbon monoxide; DPO = dendriform pulmonary ossification; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HVAC = heating, ventilation, and air conditioning; IED = improvised explosive device; M = male gender; MOS = Military Occupational Specialty Code (Army or Marines); OP = organizing pneumonia; PBM = peribronchiolar metaplasia; RV = residual volume; SMH = smooth muscle hypertrophy; TLC = total lung capacity.

[a] Deployment history includes the cumulative duration, location, and time period of military deployments to Southwest Asia, Afghanistan, the Persian Gulf, or the surrounding regions.

[b] Pulmonary function testing pattern determined using percent predicted values after adjusting for age, sex, and height based on race-neutral GLI Global standards for spirometry, lung volumes, and diffusion capacity. Obstructive pattern lung function pattern = FEV1/FVC < LLN; restrictive = TLC < lower limit of normal (LLN); air-trapping = RV > LLN; and diffusion impairment = DLCO < LLN. Numbers shown reflect percent-predicted abnormal values.

veterans following military deployments to Southwest Asia and Afghanistan. We review the known risk factors for DPO and the evidence for causal links between hazardous inhalational exposures leading to lung injury with ossification.

2. Materials and methods

We identified two sentinel cases of DPO among previously deployed military veterans with respiratory symptoms who underwent clinical evaluation in the National Jewish Health (NJH, Denver, Colorado) Deployment-Related Lung Disease Center. We queried clinical research databases at NJH and the Rocky Mountain Regional Veterans Affairs Medical Center (RMRVAMC, Aurora, Colorado) for additional cases of DPO diagnosed in veterans who were evaluated for deployment-related respiratory disease between 2012 and 2023. The privacy rights of human subjects have been observed, and all cases provided written informed consent for participation in a Research Electronic Data Capture (REDCap) database [7] with Institutional Review Board approval, BRANY HS-2689 (NJH) and COMIRB 19–1895 (RMRVAMC).

We collected information from medical records including demographics, smoking history, medical history, chest imaging, pulmonary function tests (PFT), and histopathology for all cases. Details of deployment job duties and inhalational exposures were obtained using a standardized questionnaire, supplemented with medical chart reviews. Percent predicted PFT values were calculated using race-neutral GLI Global standards [8] and abnormal physiologic patterns were defined using European Respiratory Society/American Thoracic Society (ERS/ATS) technical standards for lung function interpretation [9].

We developed a standardized chest imaging scoring form, and the most recent high-resolution chest computed tomography (CT) for each case was scored by an experienced thoracic radiologist (T.J.B.). Imaging findings of DPO required the presence of linear or branching parenchymal calcifications [10]. Extent of DPO (involving one third, two thirds, or more) and location (diffuse vs lower lobe) were assessed. Other notable findings included nodularity, emphysema, bronchial wall thickening, and pleural abnormalities.

For cases with available lung tissue, specimens were reviewed and scored by an experienced pulmonary pathologist (C.D.C.) using a standardized scoring form [11]. Findings from original pathology reports were used in those cases where tissue samples were unavailable for review.

3. Results

3.1. Initial case presentations

Five cases of DPO were identified in military veterans (Table 1). All had been referred for persistent respiratory symptoms following military deployment to Southwest Asia or Afghanistan.

Case 1. A 32-year-old Army veteran presented for evaluation of exertional shortness of breath, wheezing, chest tightness, and cough with green sputum that began in 2010 following his military deployment to Iraq.

Case 2. A 54-year-old Air Force veteran presented for evaluation of chest and throat tightness that started after his military deployment to Iraq in 2004. He also reported scant hemoptysis with exercise starting four years after his deployment and intermittent chest pain six years later. He had one previous bout of pneumonia treated with azithromycin.

Case 3. A 49-year-old Air Force veteran presented for evaluation of progressive exertional shortness of breath, chest congestion, sore throat, cough with green phlegm, and fatigue starting in 2008 following numerous military deployments to Southwest Asia. He reported being treated later for multiple bouts of pneumonia. His symptoms did not improve following empiric treatment with bronchodilators.

Case 4. A 46-year-old Army veteran presented for evaluation of exertional shortness of breath, non-productive cough, and wheezing that started in 1992 following his First Gulf War deployment to Iraq. He reported modest alleviation in his symptoms with bronchodilator use prior to exercise.

Case 5. A 64-year-old Marines veteran presented for evaluation of exertional shortness of breath, decreased exercise capacity, chest discomfort, and wheezing that began a few months after returning from deployment to the Persian Gulf. A few years later, he also developed hypoxemia and was diagnosed with constrictive bronchiolitis. His hypoxemia resolved following treatment with prednisone (80 mg daily), mycophenolate, and azithromycin. However, his respiratory symptoms continued to persist despite pharmacologic treatment.

3.2. Demographics and exposure history

All five cases were male with mean age 49 years [range: 32–64] at diagnosis of DPO, and four reported never smoking tobacco products (Table 1). For military service branch, two were in the Air Force, three in the Army/Marines. The median duration of deployment was 29 months (range 2 months–3.75 years). Three cases were deployed in the post-9/11 era of conflict, one during the First Gulf War, and one during both Gulf Wars. All reported spending over half of their deployment time outdoors, with daily exposure to diesel particulates and frequent (daily or more than 2 days per week) exposure to nearby smoke from burn pits. All reported more than monthly exposure to sandstorms. Other exposures reported by two or more of the cases included dust from explosive blasts, mortar fire or controlled detonations, and smoke from oil well fires.

3.3. Relevant comorbidities

Two cases had either silent aspiration (Case #3) or gastroesophageal reflux (GERD) to the level of the throat (Case #4) identified on diagnostic testing. All reported a history of obstructive sleep apnea (OSA). No cases had diagnoses of neurologic disorders or pulmonary fibrosis. Case #2 had a previous spontaneous pneumothorax requiring chest tube thoracostomy. None of the cases had chronic kidney disease.

3.4. Pulmonary physiology and chest imaging

PFTs and chest imaging scoring are shown in Table 1. Cases #1-4 had restrictive lung disease based on total lung capacity (TLC) less than the predicted lower limit of normal (LLN), and cases #3 and #4 had reduced diffusion capacity. Case #5 had an abnormally elevated residual volume (RV). On chest imaging, four cases had DPO involving one third of the lung in a lower-lobe predominant distribution, while one had extensive, diffuse DPO involvement (Fig. 1). Bronchial wall thickening and air-trapping were each identified in two cases, and partially calcified branching nodularity in three cases. One case had pleural thickening. None had interstitial fibrosis, ground-glass abnormalities, or lymphadenopathy.

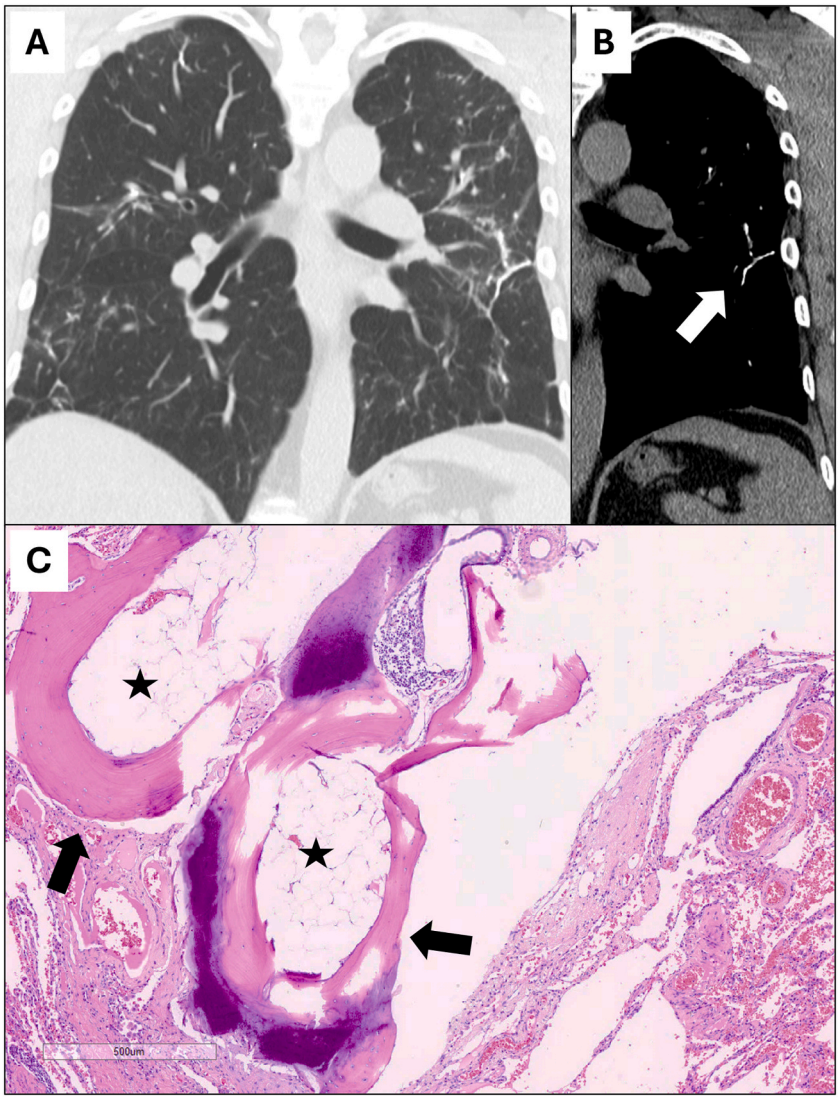

Fig. 1. Chest imaging and histology from a 49-year-old combat veteran (Case #3) with dendriform pulmonary ossification (DPO). A) Coronal chest CT (lung windows) highlighting branching nodularity and mosaic attenuation. B) Corresponding chest CT (soft-tissue windows) of the left lung showing branching parenchymal calcifications typical for DPO (arrow). C) Hematoxylin & eosin (H&E)-stained tissue section obtained from surgical lung biopsy demonstrating irregular ossification consisting of mature bone (arrow) containing marrow elements (star).

3.5. Histology

All cases had undergone lung biopsy for clinical evaluation (one transbronchial biopsy, three surgical lung biopsies, and one with both), and we were able to obtain two specimens for independent review. DPO was observed in all four cases with surgical lung biopsy (Fig. 1). Peribronchiolar metaplasia, smooth muscle hypertrophy and bronchiolitis were common. Four had organizing pneumonia, and two (both never smoked tobacco) had emphysema. Three had interstitial anthracotic pigment or retained birefringent particulate matter (consistent with retained silica/silicates). Neither transbronchial biopsy specimens showed DPO, suggesting these specimen types may be insensitive for identifying DPO. In the case with both transbronchial and surgical lung tissue (Case #3), findings of emphysema, organizing pneumonia, and DPO were demonstrated only on the larger surgical specimen.

4. Discussion

We describe five military combat veterans with confirmed DPO following Gulf War deployment. All reported substantial deployment-related inhalational exposures including burn pit emissions, smoke from oil well fires, desert dust, sandstorms, diesel particulate matter, and explosive blasts. In addition to DPO, findings of deployment-related respiratory disease including small airways abnormalities and chronic inflammation were noted [11–13]. In combination with retained lung tissue particulate matter, these abnormalities suggest substantial cumulative dust exposure in all five cases.

We examined demographic features in 91 previously published cases of DPO [2,4,5]. Compared to the median age of 49 in our case series, reported mean ages typically exceeded 65 years. In an autopsy study by Lara and colleagues [6], all eight cases of DPO were 65 years or older. Another study noted a mean age of 64 years in 43 DPO cases [14]. In five patients with biopsy-proven DPO with usual interstitial pneumonia, the mean age at diagnosis was 58 years (range 41–68) [3]. Our findings suggest that DPO may be more likely to occur in younger patients who have multiple pro-inflammatory risk factors such as OSA and GERD/aspiration in combination with exposure to known inhalational hazards.

Pathophysiologic mechanisms of DPO are poorly understood. It has been hypothesized that chronic inflammation may trigger transformation of fibroblasts to osteoblasts, with cytokine-driven cell damage that results in increased vascular permeability leading to lung calcium deposition [1]. Nodular or dendriform pulmonary ossification has been reported in up to 28.5 % of cases with idiopathic pulmonary fibrosis (IPF) and 8.3 % of cases with non-IPF fibrosis [2]. Of note, none of our five cases had findings of pulmonary fibrosis.

In the absence of concomitant interstitial fibrosis, DPO has been reported in older men with GERD, OSA, or chronic neurologic disorders that may contribute to chronic aspiration [4]. All five veterans in our case series had OSA, and two had significant reflux or silent aspiration. These co-morbidities suggest a possible interaction whereby deployment exposures may trigger or hasten the development of DPO. We postulate that inhalation of hazardous particulate matter may cause direct lung injury and/or contribute to chronic aspiration through acidic or non-acidic reflux mechanisms as described in World Trade Center responders [15,16], leading to DPO. While little is known about the natural history of DPO in this setting, and there are no evidence-based treatments, managing comorbidities and limiting ongoing exposure to hazardous particulate matter are important to minimize risk for disease progression.

Evidence linking DPO to occupational exposures is limited, and DPO in combat veterans has not been described previously. A report from Korean investigators described biopsy-confirmed DPO in a patient with pneumoconiosis from rare earth metal mining [17]. Another case report described DPO associated with 30 years of occupational asbestos exposure [5]. In a case report and review of 42 published DPO cases, 14 % reported pneumoconiosis [14]. A high index of clinical suspicion combined with a detailed occupational history may reveal additional exposure-related associations with DPO. For rare diseases such as DPO, access to large medical databases of military veterans with linkage to exposure histories may further elucidate risk factors for lung injury with ossification, paving the way for targeted prevention.

DPO may be under-recognized absent surgical lung biopsy, though diagnosis via chest imaging has improved with modern chest CT techniques [2]. One veteran in our case series reported a previous spontaneous pneumothorax that led to the diagnosis of DPO. Ten percent of incident DPO cases in another study were identified following evaluation for spontaneous pneumothorax [14]. Two DPO cases identified by Gao and colleagues had recurrent pneumothoraces [18]. As seen in other parenchymal lung diseases [19,20], architectural distortion from DPO may be a secondary cause of spontaneous pneumothorax. These findings underscore the importance of obtaining sensitive chest imaging to identify potential exposure-related lung disease in military veterans and other occupational groups following spontaneous pneumothorax.

5. Conclusion

This case series of dendriform pulmonary ossification in younger to middle aged military veterans with histories of combat deployment to Southwest Asia and Afghanistan suggests that hazardous airborne exposures may contribute to development of this rare lung disease. Clinicians should obtain a detailed occupational/environmental exposure history following diagnosis of DPO to help identify possible risk factors that may guide future prevention.

CRediT authorship contribution statement

Jeremy T. Hua: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Carlyne D. Cool:** Writing – review & editing. **Tami J. Bang:** Writing – review & editing, Formal analysis. **Silpa D. Krefft:** Writing – review & editing, Formal analysis, Data curation. **Richard C. Kraus:** Writing – review & editing, Data

curation. **Cecile S. Rose:** Writing – review & editing, Supervision, Formal analysis, Data curation, Conceptualization.

IRB approval

The privacy rights of human subjects have been observed, and all cases provided written informed consent for participation in a Research Electronic Data Capture (REDCap) database with Institutional Review Board approval, BRANY HS-2689 (NJH) and COMIRB 19–1895 (RMRVAMC).

Prior presentation

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Declaration of competing interest

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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