



Recurrent Pulmonary Embolism and Hypersensitivity Pneumonitis Secondary to *Aspergillus*, in a Compost Plant Worker: Case Report and Review of Literature

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Abstract

Activation of blood coagulation pathways as a component of an allergic response has been studied in animal models. In patients with allergic diseases, clot qualities have been noted to be different in terms of denser fibrin clot with reduced plasmin-mediated clot lysis. Correlation between occupational hypersensitivity pneumonitis (HP) with thromboembolic events is scarce in the general patient population. We present a case of a 52-year-old man with recurrent venous thromboembolism with HP secondary to bioaerosol exposure in a compost plant. Biochemical evaluation found no evidence of underlying hypercoagulable state, with only remarkable findings of elevated levels of total serum immunoglobulin E and raised *Aspergillus* sp. IgG antibodies. The patient decided to change his working environment to one without exposure to compost or other fungal elements. His symptoms and pulmonary function tests gradually improved without any subsequent intervention. The patient chose against the advice of his care providers to discontinue warfarin anti-coagulation that had been recommended for lifelong duration after recurrent pulmonary thromboembolism. At a 4-year follow-up he has remained free of any further episodes of venous thromboembolic events without any anti-coagulation. Repeated imaging studies after cessation of exposure demonstrated clearance of multiple lung nodules and improvement in DLco.

Keywords Hypersensitivity pneumonitis · Pulmonary embolism · *Aspergillus* · Pulmonary function tests · Computed tomography

Background

The pathogenesis of venous thromboembolism (VTE) and allergic reactions share risk factors and predisposing conditions [1, 2]. Activation of blood coagulation pathways as a component of an allergic response has been studied in animal models. In patients with allergic diseases (AD), clot qualities have been noted to be different in terms of denser fibrin clot with reduced plasmin-mediated clot lysis [3]. Undas et al. have demonstrated an association between atopic diseases and VTE in patients aged 45 or less, in the form of distal deep vein thrombosis (DVT) not complicated by pulmonary embolism (PE) [4]. However, correlation between occupational hypersensitivity pneumonitis (HP) with thromboembolic events is scarce in the general patient population. HP is the third most common interstitial lung disease after idiopathic pulmonary fibrosis (IPF) and non-specific interstitial pneumonia (NSIP) [5]. Although the clear criteria for diagnosing HP has been elusive for decades, recent attempt from Morisset et al. to establish a

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consensus is a great step forward [6]. Acute and chronic HP share slightly different pathophysiological pathways, inflammation being a common factor [7]. Microvascular inflammation and ischemia are known to be predisposing factors for inflammatory thrombosis [8]. We present a case of recurrent VTE in a patient with OHP secondary to compost exposure. We hypothesize that the inflammation induced by bioaerosol exposure causing HP in our patient was a temporal trigger to venous thrombotic events in our patient.

Case Presentation

A 52-year-old man with a background of working in the compost plant (from late 2007 till mid 2013) was seen in the outpatient pulmonology clinic for recurrent episodes of PE. He initially presented to his primary care provider with complaints of shortness of breath, cough, and loss of weight. He had sustained three episodes of PE (February 2008, September 2011, and February 2013) in the previous 5 years with no evident cause found. Only the first episode of PE was associated with a superficial venous thrombosis in the lower extremity after local trauma. There were no subsequent episodes of venous thrombosis. Patient was a lifelong non-smoker and had no family history of thrombo-embolic events. He had no clear precipitating factors for venous thrombosis or hypercoagulability. Each episode of PE was treated with enoxaparin and warfarin without any complications. Patient was advised to continue anti-coagulation indefinitely after his second episode of PE, when no obvious cause for PE was found.

Revisiting the history revealed occupational exposure to fungal elements, as the patient had started working in a compost plant with exposure to organic dust and bioaerosols just a few months prior to the first episode of PE. His presentation to the primary care physician at the time was typical for acute HP including weight loss, shortness of breath and significant night sweats. His symptoms had a clear temporal relation with his return to work after each episode. Despite the episodes of PE, patient continued to work at the compost plant till he had sustained his third episode of PE.

Investigations

Upon evaluation the patient was noted to have elevated levels of total serum immunoglobulin E to 495 kU/L (normal < 114 kU/L) and raised *Aspergillus* sp IgG antibodies to 3.63 (normal < 0.81 index). His IgG levels for *Cladosporium* and IgE levels for *penicillium* were negative. A HP screen, including *Saccharopolyspora*, *Saccharomonospora*, *Thermoactinomyces candidus*, and *Thermoactinomyces vulgaris* antibodies was negative. The diagnostic

workup for a hypercoagulable state, including serum protein electrophoresis, antinuclear antibodies (ANA), serum reactive plasma reagin (RPR), antineutrophil cytoplasmic antibodies (ANCA), myeloperoxidase antibody, proteinase 3 antibody and thrombophilia screen, was unrevealing. His homocysteine levels were normal, anticardiolipin antibodies were negative. Mutation analysis for Factor V Leiden and methylenetetrahydrofolate reductase (MTHFR) was negative. Prothrombin gene mutation analysis and antithrombin III levels (antigen and activity) were found to be normal. The complete blood count was normal, and eosinophilia was absent. Pulmonary function tests (PFTs) revealed mixed obstructive and restrictive lung disease with reduced total lung capacity (TLC). There was significant reduction in the diffusion capacity of carbon monoxide (DLCO). Interesting finding noted upon trending the PFTs was near normalization of diffusion capacity, TLC, and significant improvement in FEV1 after cessation of exposure to the bioaerosols (Fig. 1a, b; Table 1).

Chest radiograph in 2008 at the time of exposure to the compost and first episode of PE showed peripheral opacity in the left lower lobe (Fig. 2a). Differentials included atelectasis versus Hampton hump (pleural based opacity due to PE and infarction). Initial computed tomography (CT) of the patient demonstrated areas of PE bilaterally (Fig. 2b, c). CT chest also revealed reticulo-nodular changes involving multiple areas of the lungs bilaterally, these changes were more pronounced (Fig. 3a–c) in the next 2 years once the patient had experienced second episode of PE in 2010 (Fig. 3d). However, once patient decided to avoid the exposure to irritant organic dust, the reticulo-nodular findings on the CT scan resolved (Fig. 4a, b). Follow-up scan also confirmed clearance of clots from previous episodes of PE (Fig. 4c). Our patient did not have any broncho-alveolar lavage (BAL) during his course of illness and treatment.

Treatment

It was hypothesized, in the absence of any other measurable biochemical abnormality, that the occupational exposure could be the inciting factor for recurrent venous thrombo-embolic events.

The patient decided to change his working environment (May 2013) to one without exposure to compost or other fungal elements. His symptoms gradually improved without any subsequent intervention. The patient chose against the advice of his care providers to discontinue warfarin anti-coagulation which was recommended for lifelong duration after recurrent episodes of pulmonary thrombo-embolism.

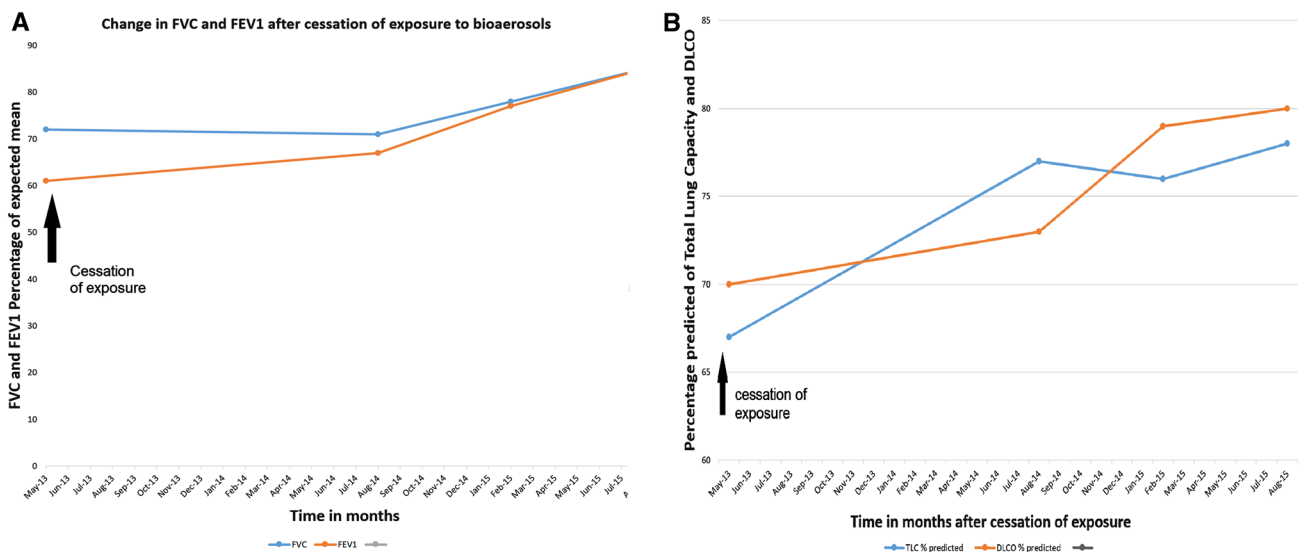


Fig. 1 **a** Trending of pulmonary function tests showing gradual and steady improvement of forced vital capacity (FVC) and FEV1. **b** Trending of pulmonary function tests showing gradual and steady

improvement of total lung capacity (TLC) and carbon monoxide diffusion capacity (DLCO)

Outcome and Follow-Up

At a 5-year follow-up he has remained free of any further episodes of venous thrombo-embolic events without any anti-coagulation. Repeated imaging studies after cessation of exposure demonstrated clearance of multiple lung nodules and PFTs done showed improvement in DLco.

Discussion

Cases have been described of occupation-induced *Aspergillus* hypersensitivity reactions amongst compost workers along with other professionals, but these incidences have not been shown to have any associated venous thrombo-embolic events [9–15]. The diagnosis of HP is challenging, as there is no gold standard test, and the diagnosis is made from a combination of clinical and biochemical features, along with the temporal association of the exposure of inciting agent at work. Returning—work provocation test provides further certainty to diagnosis [15]. This finding was strongly positive in our patient. According to a recent position paper, OHP is defined as “an immunologic lung disease with variable clinical presentation and outcome resulting from lymphocytic and frequently granulomatous inflammation which develops as a result of a non-IgE mediated allergic reaction to a variety of organic or low molecular weight agents that are present in the work environment” [16].

Morisset et al. attempted to provide a clear consensus in terms of diagnosing HP with the help of experts in this field. After rigorous survey and interview based analysis,

the diagnostic items that scored maximum were time relation with antigen exposure and disease, mosaic attenuation on chest imaging and non-necrotizing granulomas on histopathological assessment [6]. High resolution CT (HRCT) is a vital tool to aid in the diagnosis of HP. Acute HP may have normal HRCT however, with prolonged exposure it may show the predominant findings of ground-glass opacities or poorly defined small nodules. There is a significant overlap in the radiological appearance in case of sub-acute and chronic HP. Characteristic HRCT appearance in chronic HP involves a combination of reticular, ground-glass, and centrilobular nodules [7]. Minority of patients with sub-acute and chronic HP may also have thin-walled cysts resembling those seen in lymphocytic interstitial pneumonia [17, 18]. Other authors describe radio-diagnostic features of HP based on clinical and radiological subtypes. Acute or insidious type without fibrosis which demonstrates diffuse and centrilobular ground-glass opacities along with air trapping. Other type of HP noted radiologically was insidious type with fibrosis. Typical features include reticulation, peribronchovascular interstitial thickening, honey combing, and sparing of the extreme basal lung along [18, 19]. Our patient had clinical and radiological features of HP. The radiological features were more in tune with the insidious type with fibrosis (Fig. 3a–c). The diagnosis was further cemented by resolution of changes once the exposure to offending bioaerosols was discontinued.

In acute HP the PFTs initially may be normal, but with persistent exposure may result in a restrictive functional pattern. Patients may have impaired diffusion capacity (DL_{CO}), quantifiable as moderate to severe in some cases [7]. The

Table 1 Trend of lung function after cessation of *Aspergillus* exposure

	May 2013	Aug 2014	Feb 2015	Aug 2015	Mar 2017
Serial spirometric evaluations					
FVC (L)					
Pre-bronchodilator					
Mean	4.98	4.96	4.94	4.94	5.06
Actual	3.58	3.51	3.87	4.18	3.82
% Predicted	72	71	78	85	75
Post-bronchodilator					
Mean	4.98	4.96	4.94	4.94	5.06
Actual	3.45	3.72	3.61	4.10	3.94
% Predicted	69	75	73	83	77
% Change	−3	4	−5	−2	+2
FEV1 (L)					
Pre-bronchodilator					
Mean	3.98	3.96	3.93	3.93	3.89
Actual	2.44	2.67	3.04	3.34	2.95
% Predicted	61	67	77	85	75
Post-bronchodilator					
Mean	3.98	3.96	3.93	3.93	3.89
Actual	2.72	2.72	2.91	3.33	3.22
% Predicted	68	69	74	84	82
% Change	11	2	−3	−1	+8
FEV1/FVC (%)					
Pre-bronchodilator					
Mean	80	80	80	80	77
Actual	68	76	79	80	77
% Predicted	85	95	99	100	100
Post-bronchodilator					
Mean	80	80	80	80	77
Actual	79	73	81	80	82
% Predicted	99	91	101	100	106
% Change	16	−4	2	0	+6
Serial lung volumes and diffusion					
Total lung capacity (L)					
Mean (L)	7.00	7.00	7.00	7.00	7.07
Actual (L)	4.71	5.38	5.32	5.46	5.40
% Predicted	67	77	76	78	76
DLCO (mL/min/mmHg)					
Mean	36.38	36.17	35.96	35.96	36.50
Actual	25.58	26.28	28.28	28.92	28.61
% Predicted	70	73	79	80	78

diagnostic picture was strengthened by the PFTs and temporal association of these features in our patient. Although, these changes are neither sensitive nor specific to HP since most of the interstitial lung diseases with have a similar picture, but the temporal association and clinical resolution after cessation of exposure places their utility in context.

Immunopathological mechanisms for acute and chronic HP are different. Whereas the acute HP is mediated by immune complexes, the sub-acute and chronic forms of

HP are incited by T-lymphocytes, specifically Th1 immune response [20]. Asthma and COPD syndromes are also noted to be linked with increased incidence of venous thromboembolic events [21]. Local inflammation and elevated levels of IgE are known as a pro-coagulant conditions [1, 8, 22]. Inflammation and thrombosis could be a two way pathway where inflammation causes thrombosis and thrombosis subsequently worsens inflammation [23, 24]. Dugina et al. demonstrated, in a rodent model, that the activation

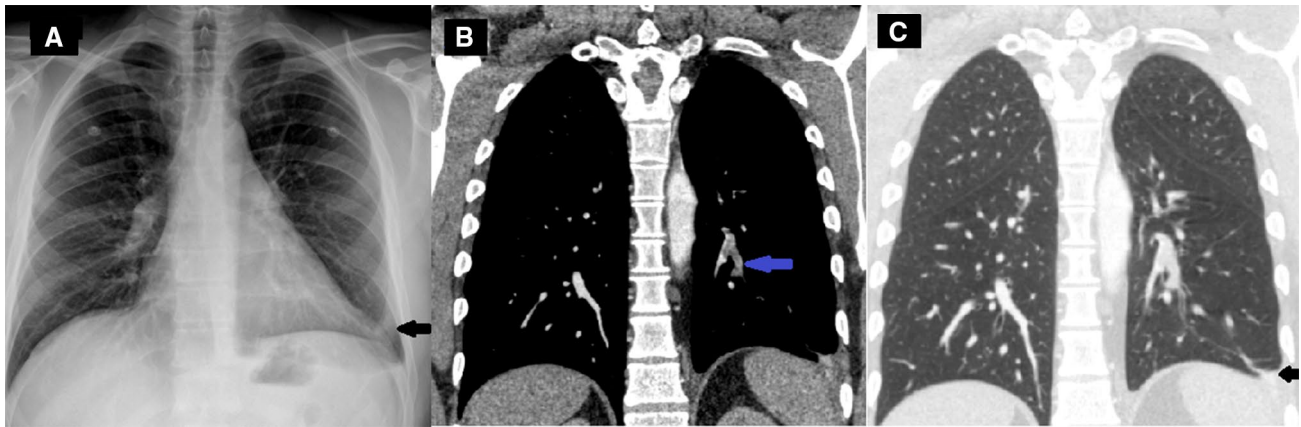


Fig. 2 **a** Initial chest radiograph in 2008 at the time of exposure to the bioaerosols. Peripheral opacity in the left lower lobe (arrow). Differentials included atelectasis versus Hampton hump (pleural based opacity due to pulmonary embolism and infarction). **b** Coronal CT

chest pulmonary embolism protocol (2008) showing central filling defect in a left lower lobe segmental pulmonary artery (arrow). **c** Coronal CT chest (lung window) showing infarction at the left lung base (arrow), corresponding to the opacity on chest radiograph

of mast cells through thrombin action on protease-activated receptors is heightened during inflammation [25]. Additionally, tryptase derived from mast cells can prompt thrombin generation through direct activation of prothrombin [26]. This generates an amplification loop. Coagulation cascade activation secondary to inflammatory response has been highlighted in other diseases such as bullous pemphigoid, angioedema associated with C1 inhibitor deficiency, rheumatoid arthritis, and sepsis [27–30]. Our case serves as an example where inflammatory response from HP, triggered secondary to exposure to organic dust at work was temporally linked to multiple episodes of VTE. Elevated levels of IgE are shown to exert prothrombotic and antifibrinolytic activity in conjunction with interaction with mast cells [1]. Moreover, many of these patient diagnosed as chronic HP go on to receive corticosteroids for a prolonged period of time, which per se are known to affect hemostasis [31, 32]. Patients with asthma have reduced platelet contractility and clot retraction rate (CRR), which predisposes asthma patients to higher odds of PE [33, 34].

In our patient the only temporally related trigger found that could have attributed to his recurrent episodes of VTE was the occupation exposure to compost. The organic dust at composting facilities is known to have high concentrations of thermophilic/thermotolerant actinomycetes and filamentous fungi [10, 35]. The pattern of respiratory illnesses among the workers in composting plants differ from other workplaces due to peculiar set of microbes. Compost workers have been reported to have higher incidences of mucosal membrane irritation (MMI) of the eyes and upper airways [13, 35–38]. Spirometric measures in our patient

showed significant reduction in the DLCO, which is noted to be the most commonly affected lung function parameter in OHP [37]. More importantly the return of diffusion capacity to almost normal after elimination of bioaerosol exposure proved to be assenting.

Our patient had documented evidence of elevated levels of *Aspergillus* IgG antibody, suggesting fungal hypersensitization as a trigger to his recurrent exacerbations of HP. Outcome was favorable with his cessation of exposure to organic dust at the composting plant, as the patient stopped having recurrences of not only HP exacerbations, but also of venous thromboembolic events over a prolonged period despite self-discontinuation of warfarin. The reason, why some people develop HP and its complications, whereas the others exposed to the same environment do not, remains unclear. The interplay of genetic susceptibility and immunopathological pathways might be accountable. The treatment of chronic and progressive HP may require empiric scheme of 0.5 mg/kg/day of prednisone for 4–6 weeks, followed by gradual taper. This is done until a maintenance dose of approximately 10 mg/day is reached [7]. However, the most important therapy remains avoidance of exposure to the pathogenic antigen [15].

This case to the best of our knowledge is the first to exhibit an association of HP due to *Aspergillus* hypersensitization and recurrent PE. Difficulty to ascertain this association as a causal relation is problematic due to an extremely small number of such occurrences. Awareness of this case will hopefully help clinicians and the exposed population to devise strategies for better outcome in similar circumstances.

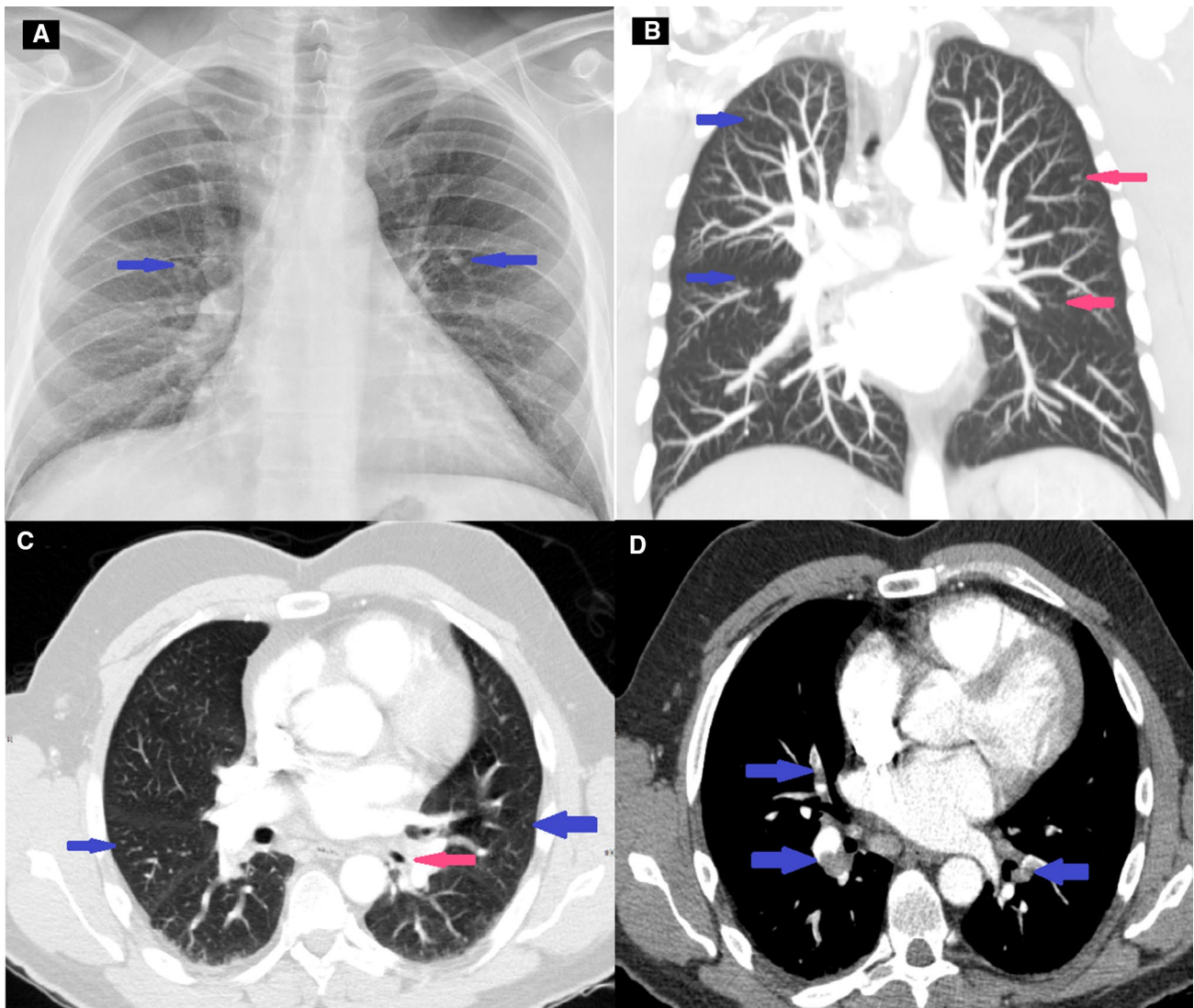


Fig. 3 **a** Chest radiograph in 2010 showing bilateral reticulo-nodular opacities in the mid lungs (arrows). **b** Coronal maximum intensity projection images showing multiple centrilobular nodules (blue arrows) and reticulations (pink arrows). Note the sparing of the lung bases. **c** Axial CT chest (lung windows) in 2010 showing mid

lung reticulonodular opacities, similar to the chest radiograph (blue arrows). Note the peribronchial thickening (pink arrow). **d** Axial chest CT, pulmonary embolism protocol in 2010 showing bilateral pulmonary emboli (arrows)

Conclusion

This case highlights novel association of occupational HP with venous thromboembolic events. Thorough work up is essential to look for the underlying cause of hypercoagulable state. In patients with unidentifiable cause of

hypercoagulable state, exposure to allergenic antigens from the organic dust may be associated PE. Work place safety measures should be accentuated to minimize the organic dust exposure causing occupational lung diseases.



Fig. 4 **a** Axial CT (lung windows) shows resolution of the reticulo-nodular pattern noted on prior CTs. **b** Coronal CT (lung windows) shows resolution of the reticulonodular pattern noted on prior CTs.

c Axial CT chest, pulmonary embolism protocol in 2013 shows resolution of filling defects in bilateral lower lobar pulmonary arteries (arrows)

Author Contributions AL: Study design, manuscript draft, and critical review of manuscript. JA: Literature review, data collection, and critical review of manuscript. HG: Literature review, data collection, and critical review of manuscript. SP: Literature review, image selection, and critical review of manuscript. KM: Inception of idea, and critical review of manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interests.

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