ECRONICON OPEN ACCESS

EC PULMONOLOGY AND RESPIRATORY MEDICINE

Case Report

# Patient with Combined Idiopathic Pulmonary Fibrosis, Thromboembolism and Obstructive Sleep Apnea

**Pierpaolo Prosperi[1], Marica Tina Maccarone[2] and Antonella Spacone FCCP[1]***

[1]*Respiratory Medicine Department, Hospital "Santo Spirito", Pescara, Italy*

[2]*Radiology Division, Hospital "Santo Spirito" Pescara", Pescara, Italy*

***Corresponding Author:** Antonella Spacone, Respiratory Medicine Department, Hospital "Santo Spirito", Pescara, Italy.

**Received:** July 08, 2019; **Published:** August 19, 2019

## Abstract

**Background:** Idiopathic pulmonary fibrosis (IPF) is associated with significant comorbidities, including pulmonary hypertension, emphysema, pulmonary lung cancer, pulmonary thromboembolism (TEP), coronary artery disease, gastroesophageal reflux disease and obstructive sleep apnea (OSA). In patients with OSA, episodes of cyclic deoxygenation-oxygenation occur; the free radicals cascade is activated and gene expression is altered, comprising a rise in the plasma levels of proflogogen substances and of adhesion molecules increasing embolic and cardiovascular risk. Also, in the IPF the balance in coagulation factors is disrupted. In light of these findings, the combination of IPF and OSA could increase the embolic risk in such patients. Our case report of a patient with IPF and OSA, who develops an embolism demonstrates a possible synergy between the 2 pathologies.

**Case Report:** E.G., a 75-year-old with a diagnosis of familiar IPF for2 years, who had been treated with antifibrotic drugs, was hospitalized for progressive dyspnea and thoracalgia resulting in a diagnosis of TEP. The search for triggering factors was negative. She was treated with fondaparinux 7.5 mg and then with apixaban.

At the clinical follow-up 2 months after discharge, the patient underwent nocturnal cardio-respiratory monitoring, from which a profile of moderate OSA emerged.

This clinical case underscores the importance of identifying comorbidities in the optimal management of IPF, to identify also the conditions of comorbidity. The pathogenetic mechanisms of OSA and IPF could have a synergistic effect on endothelial damage and thus increase the risk of embolism.

***Keywords:*** *Obstructive Sleep Apnea; Pulmonary Embolism; Idiopathic Pulmonary Fibrosis*

## Introduction

Idiopathic pulmonary fibrosis (IPF) is one of the most frequent and most severe forms of interstitial lung diseases [1,2]. It is characterized by a progressive heterogeneous course, with a median survival of 2.5 to 4.5 years and limited treatment options.

IPF is the most common form of idiopathic interstitial lung disease, with a prevalence of 14 to 63 per 100.000 [2] and is diagnosed primarily in the elderly males and ex-current smokers [3].

The disease is characterized by the progressive worsening of lung function, significantly affecting health-related quality of life and has been associated with many comorbidities such as pulmonary hypertension, emphysema, lung cancer, coronary artery disease, diastolic dysfunction, gastroesophageal reflux disease, sleep disorders, endocrine disorders and psychiatric disturbances [4-20]. Although a link between development of thromboembolism (TEP) and IPF has not been definitively established, it appears that there is an increased risk

of venous thromboembolism (VTE) and pulmonary embolism in those with IPF [21]. Possible molecular etiopathogenetic mechanisms include activation of the coagulation cascade, via the tissue factor-dependent extrinsic pathway and as evidenced by elevated levels of tissue factor and fibrin, as seen in lung tissue from patients with IPF [22]. Threre are also abnormalities in intrinsic anticoagulation pathways (likely decreased protein C activation) and fibrinolysis appears to be dysregulated [23].

Obstructive sleep apnea (OSA) is a disease, that is characterized by frequent episodes of upper airway collapse during sleep, associated with intermittent arterial oxygen desaturation.

OSA is also being recognized as an independent risk factor for several clinical comorbidities, including systemic hypertension, cardiovascular disease, stroke, and abnormal glucose metabolism and VTE [24]. Intermittent hypoxia, present in OSA, is responsible for the oxidative stress and inflammatory response that can in turn alter endothelial function and increase intravascular coagulation, potential pathogenetic mechanisms of TEP [25].

It has been suggested that in subjects with OSA hypercoagulability depends on increases in factor XIIa, factor VIIa, thrombin-antithrombin complex, tissue factor, plasma fibrinogen and patelet activity [26,27]. OSA can cause hemodynamic disturbances due to decreased venous return and damage to vascular endothelial structure [27].

## Case Report

E.G., a 75-year-old female (non-smoker, body mass index: 25 $Kg/m^2$) with a diagnosis of familial IPF for 2 years, who was treated with antifibrotic drugs was hospitalized for progressive dyspnea and thoracalgia.

The patient had hypoxemia with modest hypocapnia ($PaO_2$ 54.2 mmHg, $PaCO_2$ 30.2 mmHg pH 7.50, $SatO_2$ 86%) and underwent radiography of the chest in 2 projections, which was negative; the phlogosis and D dimer indices were increased.

Thus, the patient, who had a history of allergic diathesis to an iodinated contrast agent, was subjected to diagnostic completion with perfusion scintigraphy, which t revealed nonhomogeneous uptake of the tracer (99m-TC) in the apical segment of the right inferior pulmonary lobe and a hypoperfusion triangle-shaped area is identified on the apical segment of the right pulmonary lobe (suggestive of pulmonary infarction (Figure 1 and 2). These exam findings were consistent with TEP.

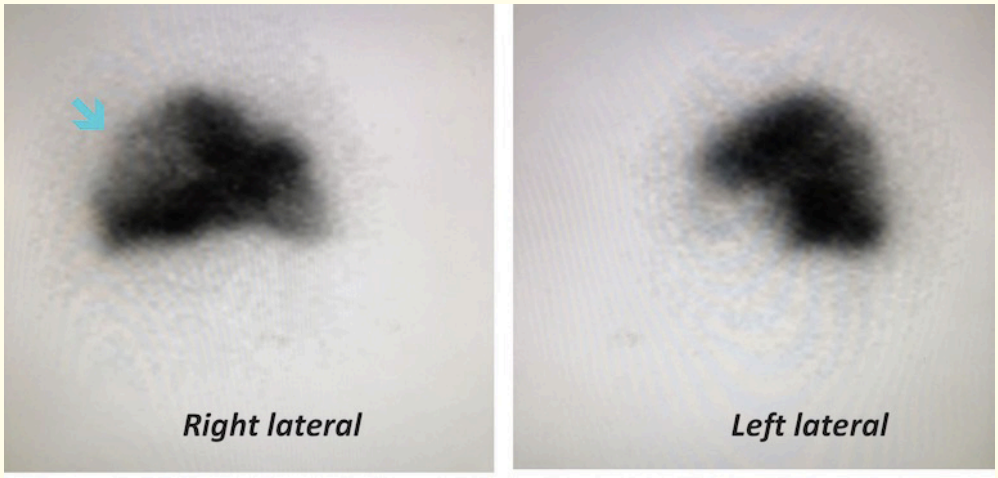


***Figure 1:*** *Imagine of perfusion scintigraphy: lateral image: abnormal tracing, cold spot suggestive of pulmonary embolism on the apical segment of the right inferior pulmonary lobe.*

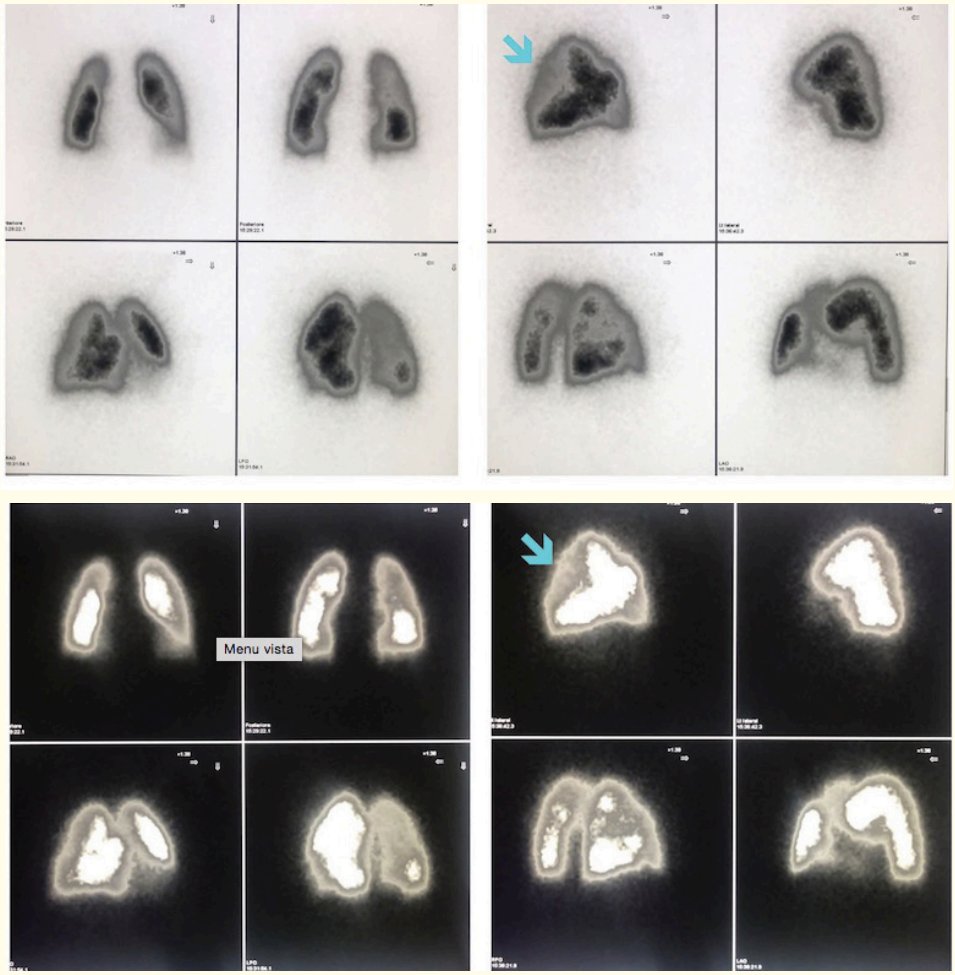


***Figure 2:*** *Imagines of perfusion scintigraphy: an hypoperfusion triangle-shaped area is identified on the apical segment of the right inferior pulmonary lobe suggestive of pulmonary infarction.*

In the medical history of patient were absent the risk factors such having high blood pressure, having had recent injury or trauma to a vein, having burns or fractures of the hips or thigh bone and having been inactive or immobile for long periods time.

The determinations of antiphospholipid-dependent antibodies, beta2 glycoprotein, antibodies anticardiolipin and lupus anticoagulant were normal. Hereditary thrombotic risk factors were also determined: homocysteine, mutations of factor V, mutation factor II, anti-thrombin, protein C, protein S and other laboratory tests were all normal.

Doppler ultrasonography of the legs, echocardiography and neoplastic markers were found to be negative.

The patient was treated with oxygentherapy, fondaparinux 7.5 mg and then apixaban 10 mg bid for first 7 days, after 5 mg bid. The arterial blood gas analysis without oxygen performed at discharge showed $PaO_2$ 68 mmHg, $PCO_2$ 43 mmHg and pH 7.40.

At the clinical follow-up 2 months after discharge, due to reported excessive daytime sleepiness and weakness, snoring, disturbed night sleep and morning headaches, the patient underwent a home sleep apnea test (HSAT) overnight in room air.

Apneas, hypopneas, and apnea-hypopnea index (AHI) were defined according to current criteria [28. Other parameters that were analyzed were: respiratory disturbance index (RDI), events and number of events of obstructive apneas (OA) and central apnea (CA), number and events of hypopnea (H), mixed (M), oxygen desaturation index (ODI) and average of arterial saturation ($SpO_2$ average%) with time of desaturation (T < 90%).

The exam revealed a moderate OSA (AHI 19.9/h, severe in supine position (AHI 32.3/h), several prolonged episodes of obstructive sleep apnea -118 apnea and hypopnea (A+H) events,- 5 obstructive apnea events and 113 hypopnea with a mean duration of 17 sec and an average of arterial saturation of 91.7% (Table 1).

| | **Diagnostic** |
|---|---|
| AHI (Events/h) | 19.9 |
| AHI supine (Events/h) | 32.3 |
| OA Events/h | 5 |
| CA Events/h-N° events | 1-1 |
| H Events/h - N° events | 18-113 |
| Apnea (median duration) (sec) | 12 |
| Hypopnea (median duration) (sec) | 17 |
| $SpO_2$ average (%) | 91.7 |
| T<90% | 12 |
| ODI Events/h | 20.3 |

***Table 1:*** *HSAT values.*

The patient, at a subsequent examination, had a Mallampati score of 4. She, then underwent with continuous positive airway pressure (CPAP) therapy which had benefit and corrected her polygraphic indexes.

## Discussion

IPF is a rare form of fibrotic lung disease with no known etiology that progresses over the course of several years. It is characterized by scar tissue formation within the lungs, dyspnea, and a significantly shortened lifespan after diagnosis [1]. Although its etiology is unknown, several potential risk factors have been described such as cigarette smoking, certain types of environmental exposures, microbial agents, gastroesophageal reflux [1,2].

The therapy comprises antifibrotic agents:and should be accompanied by supportive measures, including smoking cessation, pulmonary rehabilitation, and supplemental oxygen when appropriate [3].

IPF is associated with a wide range of respiratory and non-respira- tory conditions, such as gastroesophageal reflux, cardiovascular disease, pulmonary hypertension, lung cancer, obstructive sleep apnea, depression and diabetes [4-20]. The presence of comorbidities in IPF can significantly influence the prognosis and guide management strategies: thus clinicians must recognize the potential for these concurrent conditions and be able to identify and manage them. Sleep-related disorders are increasingly considered important comorbidities in IPF patients. Sleep in IPF patients is associated with a degree of hypoventilation and moderate to severe OSA syndrome, defined as an apnea–hypopnea index (AHI) > 15 events per hour [26,27].

OSA canappear during the natural course of the interstitial lung disease, as a consequence of lung function restriction, or it can promote gastroesophageal reflux disease or increase oxidative lung stress through chronic nocturnal intermittent hypoxia: these mechanisms can per se increase the risk for interstitial lung disease [29-31]. The repeated episodes of hypoxia and normoxia, present in OSA are reminiscent of ischemia reperfusion events, and these conditions are believed to upregulate reactive oxygen species (ROS) and oxidative stress and cause ischemia-reperfusion injury to the vascular wall, increasing the risk for atherosclerosis and consequently TEP [27].

In IPF the balance in coagulation factors is altered and the with risk of VTE and TEP is higher. There is clinical evidence that IPF is associated with a prothrombotic state. In a case control study, 80% of patients with IPF were in a prothrombotic state (defined as the presence of at least 1 inherited or acquired clotting defect or marker of fibrinolytic dysfunction) [4]. The hypercoagulable state is present in IPF and OSA; its causes include hemodynamic alterations, oxidative stress, systemic inflammation, hypercoagulability and vascular endothelial dysfunction.. We have presented a patient with IPF, who was with antifibrotic drug and had undiagnosed OSA but developed TEP. Excluding the presence of other risk factors for TEP the patient was referred for HSAT, which revelaled moderate OSA.

## Conclusion

The coexistence of OSA and IPF could have a synergic effect in increasing the risk of developing TEP. An earlier diagnosis of IPF is prerequisite for timely treatment and, potentially, improved of the long-term clinical outcomes of this progressive and ultimately fatal disease. All associated comorbidities in IPF must be recognized and treated early. This represents a significant challenge for the pulmonologist who was specializes in interstitial lung diseases.

## Acknowledgments

None.

## Conflict of Interests

All authors declare that they have no competing interests.

## Bibliography

1. King SJ and Natan SD. "Idiopathic pulmonary fibrosis: effects and optimal management of comorbidities". *Lancet Respiratory Medicine* 5.1 (2017): 72-84.

2. Ley B and Collard HR. "Epidemiology of idiopathic pulmonary fibrosis". *Clinical Epidemiology* 25.5 (2013): 483-492.

3. Behr J., *et al*. "Management of patients with idiopathic pulmonary fibrosis in clinical practice: the INSIGHTS-IPF registry". *European Respiratory Journal* 46.1 (2015): 186-196.

4. Ley B., *et al*. "Clinical course and prediction of survival in idiopathic pulmonary fibrosis". *American Journal of Respiratory and Critical Care Medicine* 183.4 (2011): 431-440

5. Lettieri CJ., *et al*. "Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis". *Chest* 129.3 (2006): 746-752.

6. Hamada K., *et al*. "Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis". *Chest* 131.3 (2007): 650-656.

7. Patel NM., *et al*. "Pulmonary hypertension in idiopathic pulmonary fibrosis". *Chest* 132.3 (2007): 998-1006.

8. Mejía M., *et al*. "Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension". *Chest* 136.1 (2009): 10-15.

9. Cottin V., *et al*. "Combined pulmonary fibrosis and emphysema: a distinct under recognised entity". *European Respiratory Journal* 26.4 (2005): 586-593.

10. Kreuter M., *et al*. "Treatment and outcome of lung cancer in idiopathic interstitial pneumonias". *Sarcoidosis Vasculitis and Diffuse Lung Disease* 31.4 (2015): 266-274.

11. Tomassetti S., *et al*. "The impact of lung cancer on survival of idiopathic pulmonary fibrosis". *Chest* 147.1 (2015): 157-164.

12. Nathan SD., *et al*. "Prevalence and impact of coronary artery disease in idiopathic pulmonary fibrosis". *Respiratory Medicine* 104.7 (2010): 1035-1041.

13. Kizer JR., *et al*. "Association between pulmonary fibrosis and coronary artery disease". *Archives of Internal Medicine* 164.5 (2004): 551-556.

14. Papadopoulos CE., *et al*. "Left ventricular diastolic dysfunction in idiopathic pulmonary fibrosis: a tissue Doppler echocardiographic [corrected. Study". *European Respiratory Journal* 31.4 (2008): 701-706.

15. 15.Lee JS., *et al*. "Gastroesophageal reflux therapy is associated with longer survival in patients with idiopathic pulmonary fibrosis". *American Journal of Respiratory and Critical Care Medicine* 184.12 (2011) 1390-1394.

16. 16.Lee JS., *et al*. "Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: An analysis of data from three randomised controlled trials". *Lancet Respiratory Medicine* 1.5 (2013): 369-376.

17. Krishnan V., *et al*. "Sleep quality and health-related quality of life in idiopathic pulmonary fibrosis". *Chest* 134.4 (2008): 693-638.

18. 18.Lancaster LH., *et al*. "Obstructive sleep apnea is common in idiopathic pulmonary fibrosis". *Chest* 136.3 (2009): 772-778.

19. Mermigkis C., *et al*. "Sleep-related breathing disorders in patients with idiopathic pulmonary fibrosis". *Lung* 185.3 (2007): 173-178.

20. De Vries J., *et al*. "Quality of life of pulmonary fibrosis patients". *European Respiratory Journal* 17.5 (2001): 954-961.

21. Hubbard RB., *et al*. "The association between idiopathic pulmonary fibrosis and vascular disease". *American Journal of Respiratory and Critical Care Medicine* 178 (2008): 1257-1261.

22. Imokawa S., *et al*. "Tissue factor expression and fibrin deposition in the lungs of patients with idiophatic pulmonary fibrosis and systemic sclerosis". *American Journal of Respiratory and Critical Care Medicine* 156 (1997): 631-636.

23. Kobayashi H., *et al*. "Protein C anticoagulant system in patients with interstitial lung disease". *American Journal of Respiratory and Critical Care Medicine* 157 (1998): 1850-1854.

24. Pinto JA., *et al*. "Comorbidities associated with Obstructive Sleep Apnea: a Retrospective Study". *International Archives of Otorhinolaryngology* 20.2 (2016): 145-150.

25. Feng J., *et al*. "Endothelial mechanisms of endothelial dysfunction in patients with obstructive sleep apnea". *Sleep Breath* 16 (2012): 283-294.

26. Kanel RV and Loredo JS. "Association between polysomnographic measures of disrupted sleep and prothrombotic factors". *Chest* 131 (2007): 733-739.

27. Badhiraja R., *et al*. "Endothelial dysfunction in obstructive sleep apnea". *Journal of Clinical Sleep Medicine* 3 (2007): 409-415.

28. Kapur V.K., *et al*. "Harrod C.G. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline". *Journal of Clinical Sleep Medicine* 13.3 (2017): 479-504.

29. Mermigkis C., *et al*. "Obstructive sleep apnea should be treated in patients with idiopathic pulmonary fibrosis". *Sleep Breath* 19 (2015): 385-391.

30. Mermigkis C., *et al*. "Sleep as a new target for improving outcomes in idiopathic pulmonary fibrosis". *Chest* 152.6 (2017): 1327-1338.

31. Cano-Jimenez E., *et al*. "Comorbidities and complications in idiophatic pulmonary fibrosis". *Medical Sciences* 30.6 (2018): 71-84.

**Volume 8 Issue 9 September 2019**