Research Article

# A Rare Coexistence Of Asthma-COPD Overlap Syndrome and Obstructive Sleep Apnea With Restless Leg Syndrome and Thrombocytopenia: A Case Report

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**ABSTRACT**

**Background:** Overlap syndrome, defined by the coexistence of asthma-COPD overlap syndrome (ACOS) with obstructive sleep apnea (OSA), involves shared pathophysiological mechanisms including airway inflammation, systemic inflammation, and altered respiratory mechanics. Restless leg syndrome (RLS) is reported in 15–30% of patients with overlap syndrome, while thrombocytopenia remains a rarely documented association in this clinical context.

**Case Presentation:** A 63-year-old male presented with progressive dyspnea (mMRC grade 3) and nocturnal awakenings with tingling sensations and an irresistible urge to move his legs. He had poorly controlled persistent bronchial asthma with an ACT score of 9. Spirometry showed a pre-bronchodilator FEV1 of 50.5% predicted and FEV1/FVC of 54.4%, with minimal improvement following 2 µg salbutamol (FEV1 51.8%; FEV1/FVC 55.1%), confirming poor bronchodilator reversibility below both the 12% and 200 mL thresholds. High-resolution computed tomography confirmed centrilobular emphysema. Polysomnography demonstrated an apnea-hypopnea index of 29.3 events/hour with 137 hypopneas (19.8/hour), 65 apneas including one central apnea, and a nadir oxygen saturation of 78%, consistent with moderate-to-severe OSA. Serum IgE was elevated at 385.40 IU/mL and platelet count was 105,000/cmm. Autoimmune, infectious, and abdominal imaging workup were unremarkable. RLS was confirmed using all five IRLSSG diagnostic criteria.

**Conclusion:** This case highlights the rare coexistence of ACOS, OSA, RLS, and thrombocytopenia in a single patient. Chronic intermittent hypoxia and systemic inflammation appear to serve as central mechanistic links. Comprehensive multidisciplinary evaluation is essential in overlap syndrome, and further studies are needed to define the prevalence and pathophysiological basis of thrombocytopenia in this setting.

**Keywords:** Asthma-COPD Overlap Syndrome · Obstructive Sleep Apnea · Restless Leg Syndrome · Thrombocytopenia · Hypoxia · Systemic Inflammation · Overlap Syndrome.

## INTRODUCTION

Asthma-COPD overlap syndrome (ACOS) is characterized by persistent airflow limitation with features shared by both asthma and chronic obstructive pulmonary disease (COPD), affecting an estimated 15–20% of COPD patients [1]. It is distinguished by eosinophilic airway and systemic inflammation, partially reversible obstruction, and heightened exacerbation frequency compared to COPD alone [1]. When ACOS coexists with OSA, a further dimension of respiratory compromise is introduced, with shared mechanisms including upper and lower airway inflammation, altered respiratory mechanics, and nocturnal hypoxemia [2]. The overlap of asthma with OSA has been recognized as a distinct clinical endophenotype, characterized by nocturnal bronchial hyperresponsiveness, autonomic dysfunction, and reduced asthma control [3]. Collectively, the coexistence of ACOS and OSA — sometimes termed a "triple overlap" — confers a greater burden of exacerbations and hospitalization than either condition alone [4].

Within this framework, RLS is an increasingly recognized comorbidity. Among patients with COPD and OSA, RLS prevalence ranges from 10% to 30%, driven by intermittent hypoxia, sleep fragmentation, and disruption of dopaminergic pathways [5,6]. A recent systematic review confirmed that comorbid RLS and OSA constitute a clinically distinct phenotype with a greater symptom burden and more complex therapeutic trajectories [7]. Thrombocytopenia, however, is far less commonly reported in this context. Doganci and Eraslan Doganay demonstrated that thrombocytopenia carries significant prognostic implications in COPD patients with acute exacerbations, with hypoxia and systemic inflammation identified as key contributing mechanisms [8].

The simultaneous occurrence of ACOS, OSA, RLS, and thrombocytopenia in a single patient has not been previously documented in the literature. This case report aims to describe this rare clinical constellation and

explore the shared pathophysiological mechanisms underlying these conditions, underscoring the need for comprehensive multidisciplinary evaluation in overlap syndrome.

## CASE PRESENTATION

A 63-year-old male presented to the respiratory clinic with progressive dyspnea graded mMRC 3 and nocturnal awakenings associated with tingling sensations and an irresistible urge to move his legs. He carried a longstanding diagnosis of persistent bronchial asthma that remained poorly controlled despite ongoing treatment with inhaled corticosteroids and bronchodilators, as evidenced by an ACT score of 9 out of 25. There was no prior documented diagnosis of RLS or any hematological disorder.

Spirometry demonstrated a pre-bronchodilator FEV1 of 50.5% predicted and an FEV1/FVC ratio of 54.4%, consistent with an obstructive ventilatory pattern. Following administration of 2 µg salbutamol, only minimal improvement was observed, with FEV1 rising to 51.8% and FEV1/FVC to 55.1%, an increment falling below both the 12% relative and 200 mL absolute thresholds for significant bronchodilator reversibility, satisfying criteria for a fixed obstructive defect. High-resolution computed tomography of the chest demonstrated centrilobular emphysema, providing radiological confirmation of the COPD component and establishing the diagnosis of ACOS.

Polysomnography revealed an apnea-hypopnea index of 29.3 events/hour, comprising 137 hypopnea events at a rate of 19.8 per hour and 65 apnea events, of which one was central, with a nadir oxygen saturation of 78%, confirming moderate-to-severe OSA with significant nocturnal desaturation. All respiratory investigations and sleep study findings are summarized in Table 1.

Laboratory evaluation revealed a mildly elevated serum IgE of 385.40 IU/mL, supportive of the atopic component of asthma, and a platelet count of 105,000/cmm, consistent with mild thrombocytopenia. A comprehensive secondary workup including autoimmune screening, infectious disease testing, and abdominal imaging was unremarkable, with no evidence of splenomegaly or portal hypertension, effectively excluding autoimmune, infectious, and hypersplenism-related etiologies. The complete laboratory and imaging findings are presented in Table 1.

**Table 1: Summary of Investigations**

| Domain | Investigation | Finding | Interpretation |
|---|---|---|---|
| **Pulmonary Function** | Spirometry (pre-BD) | FEV1 50.5%; FEV1/FVC 54.4% | Obstructive pattern |
| **Pulmonary Function** | Spirometry (post-BD, 2 µg salbutamol) | FEV1 51.8%; FEV1/FVC 55.1% | Poor reversibility (<12%, <200 mL) |
| **Imaging** | HRCT Chest | Centrilobular emphysema | Confirms COPD component |
| **Sleep Study** | Polysomnography | AHI 29.3/hr; hypopneas 137 (19.8/hr); apneas 65 (1 central); $SpO_2$ nadir 78% | Moderate-to-severe OSA |
| **Laboratory** | Serum IgE | 385.40 IU/mL | Elevated; supports atopic component |
| **Laboratory** | Platelet count | 105,000/cmm | Mild thrombocytopenia |
| **Laboratory** | Autoimmune panel | Unremarkable | Excludes autoimmune etiology |
| **Laboratory** | Infectious workup | Unremarkable | Excludes infectious etiology |
| **Imaging** | Abdominal imaging | Unremarkable | No splenomegaly/portal hypertension |

RLS was formally diagnosed using the International Restless Leg Syndrome Study Group (IRLSSG) criteria. The patient fulfilled all five mandatory diagnostic criteria, as presented in Table 2, with nocturnal leg discomfort and an irresistible urge to move, worsening at rest, partial relief with movement, predominant evening and nocturnal exacerbation, and no alternative condition fully accounting for the symptoms.

**Table 2: IRLSSG Diagnostic Criteria — Assessment in This Patient**

| Criterion | Description | Present in This Patient |
|---|---|---|
| **1** | Urge to move legs, usually with uncomfortable sensations | Present |

| | | |
|---|---|---|
| **2** | Symptoms begin or worsen during rest or inactivity | Present |
| **3** | Symptoms partially or totally relieved by movement | Present |
| **4** | Symptoms worse in the evening or night | Present |
| **5** | Not solely accounted for by another condition | Present |

On the basis of the complete clinical, functional, polysomnographic, and laboratory evaluation, a final diagnosis of ACOS, moderate-to-severe OSA, RLS, and mild thrombocytopenia of likely hypoxia- and inflammation-mediated etiology was established. Management was initiated with CPAP therapy for OSA, optimized inhaled pharmacotherapy comprising an ICS/LABA/LAMA combination for ACOS, dopamine agonist therapy for RLS, and regular hematological follow-up for platelet count monitoring.

## DISCUSSION

The present case demonstrates the rare coexistence of ACOS, moderate-to-severe OSA, RLS, and thrombocytopenia, offering a unique lens through which to examine their shared pathophysiological underpinnings.

The spirometric findings in this patient — a pre-bronchodilator FEV1/FVC of 54.4%, minimal post-bronchodilator improvement following 2 µg salbutamol, and centrilobular emphysema on HRCT — collectively established the COPD component, while elevated IgE of 385.40 IU/mL and longstanding poorly controlled asthma confirmed the atopic component of ACOS. Kume et al. demonstrated that eosinophilic airway inflammation complicates up to 50% of COPD cases without overt asthma, underscoring the mechanistic continuity between atopic and obstructive airway disease [9]. Poor bronchodilator reversibility, as observed in this patient, is a recognized distinguishing feature of ACOS from pure asthma, reflecting fixed structural remodelling characteristic of COPD [1]. The additional diagnosis of OSA, evidenced by an AHI of 29.3 events/hour and a nadir $SpO_2$ of 78%, created a "triple overlap" that substantially amplified nocturnal respiratory compromise. Kendzerska et al., in a large prospective cohort study, demonstrated that co-occurrence of nocturnal hypoxemia with COPD increased the hazard of cardiovascular events and all-cause mortality nearly twofold compared to either condition alone [10], contextualizing the systemic severity of this patient's presentation.

The RLS symptoms in this case — nocturnal leg discomfort, an irresistible urge to move, and relief with movement, fulfilling all five IRLSSG criteria — are consistent with the well-established association between RLS and sleep-disordered breathing. Intermittent hypoxia, as evidenced by the nadir $SpO_2$ of 78% recorded on polysomnography, disrupts dopaminergic signalling in the spinal cord, which constitutes the central neurochemical mechanism underlying RLS [5]. Kim et al. found RLS in 16.1% of OSA patients, with RLS severity inversely correlated with AHI and nadir oxygen saturation, suggesting that the degree of hypoxic burden directly modulates sensorimotor symptom severity [6]. The Co-ROSA systematic review further confirmed that comorbid RLS and OSA represent a clinically distinct phenotype with a greater symptom burden, and that CPAP therapy led to meaningful RLS improvement in over 70% of patients across several cohorts by correcting the underlying hypoxic milieu [7]. Critically, the most recent clinical practice guideline from the American Academy of Sleep Medicine explicitly identifies untreated OSA as a primary exacerbating factor for RLS, recommending its correction as an essential first management step [13].

The finding of mild thrombocytopenia in the absence of autoimmune, infectious, or structural causes in this patient is best explained by the dual insult of chronic intermittent hypoxia and systemic inflammation inherent to overlap syndrome. Gabryelska et al. described how intermittent hypoxia in OSA drives platelet hyperactivation and phenotypic alteration through oxidative stress and inflammatory cytokine release, resulting in accelerated platelet consumption [11]. Chen et al. corroborated that OSA-related hypoxia upregulates P-selectin and thromboxane pathways, further dysregulating platelet homeostasis [12]. In the context of COPD, Doganci and Eraslan Doganay demonstrated that thrombocytopenia was associated with a 61.5% mortality rate in patients admitted to the intensive care unit, identifying hypoxia-mediated bone marrow suppression and systemic inflammation as the primary etiological drivers [8]. In the present case, the chronic hypoxic and inflammatory burden likely impaired thrombopoiesis while simultaneously accelerating platelet consumption, culminating in mild but clinically noteworthy thrombocytopenia.

The central mechanistic thread linking all four conditions is chronic intermittent hypoxia and systemic low-grade inflammation — forces that simultaneously disrupt dopaminergic pathways, impair bone marrow thrombopoiesis, perpetuate airway remodelling, and destabilize upper airway tone. From a diagnostic standpoint, the overlapping symptomatology of dyspnea, fatigue, and sleep disruption can readily obscure the individual contributions of each condition, particularly RLS and thrombocytopenia, which are seldom evaluated in routine respiratory assessments. Marin-Oto and Marin highlighted that OSA in chronic airway disease remains

a frequently missed diagnostic opportunity, with direct consequences for exacerbation burden [4]. Therapeutically, CPAP carries the potential to simultaneously address OSA-related hypoxia, attenuate RLS severity, and reduce pathological platelet activation, while an optimized ICS/LABA/LAMA regimen targets the airway inflammatory component of ACOS, underscoring the indispensability of a unified, multidisciplinary management approach.

## CONCLUSION

This case illustrates the rare and clinically significant coexistence of ACOS, OSA, RLS, and thrombocytopenia in a single patient. Chronic intermittent hypoxia and systemic inflammation emerge as the central mechanistic threads linking these conditions, contributing to dopaminergic dysfunction underlying RLS and disrupted thrombopoiesis resulting in thrombocytopenia. The absence of any identifiable secondary cause for thrombocytopenia further supports hypoxia and inflammation as the primary contributors. This case underscores the necessity of a comprehensive, multidisciplinary approach in the evaluation and management of overlap syndrome, extending beyond the respiratory system to encompass neurological and hematological manifestations. Future epidemiological and mechanistic research is warranted to establish the true prevalence and pathophysiological basis of thrombocytopenia in overlap syndrome.

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