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CASE REPORT

Obstructive Sleep Apnea in a Patient with Pulmonary Thromboembolism

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ABSTRACT

Pulmonary embolism (PE) is a major manifestation of venous thromboembolism (VTE). Obstructive sleep apnea (OSA) leads to hypercoagulable state and may be associated with recurrent PE in the absence of deep vein thrombosis (DVT). Early identification and treatment of OSA may be helpful in reducing the recurrence of PE. Here, we report a case of OSA presenting with isolated PE without DVT with a brief mention of therapeutic implications.

Keywords: Obstructive sleep apnoea, Pulmonary embolism, Pulmonary thromboembolism.

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CASE REPORT

A 58-year-old male patient presented with complaints of exertional dyspnea of modified Medical Research Council (MMRC) Grade I for 2 years. Since 2 months, the patient had gradual deterioration and dyspnea progressed to MMRC Grade IV prior to presentation. Patient denied any history of chest pain, cough, hemoptysis, wheeze, snoring, excessive day time sleepiness, fever, loss of weight and appetite. Patient also denied history of trauma, major surgery, prolonged immobilization, malignancy and long-distance travel in sitting posture. He was previously a diagnosed case of coronary artery disease 6 years back and was on regular treatment with antiplatelet drugs. He was a former smoker with 20 pack years of smoking, who had quit smoking 15 years back. He denied alcohol and illicit drug use. He was an ex-army officer by occupation. Prior to presentation to our institute for further evaluation and management, patient was evaluated in regional service hospital. Investigations revealed polycythemia with hemoglobin of 18.9 gm/dL and hematocrit of 55 with other blood counts being normal. Serum erythropoietin was raised, JAK 2 V617F and exon 2 mutations were negative, and bone marrow biopsy was normocellular with trilineage hematopoiesis. Patient had also received two episodes of phlebotomy outside in view of polycythemia. Other biochemical analysis reports and pulmonary function tests were within normal limits.

On presentation to our institute, the patient was afebrile and on examination at rest, pulse rate was 105/minute, respiratory rate 32/minute, blood pressure was 118/70 mm Hg, and peripheral capillary oxygen saturation was 95% on room air. Auscultation revealed bilateral vesicular breath sounds. Arterial blood gas analysis on fraction of inspired oxygen of 0.21 showed respiratory alkalosis with moderate hypoxemia with widened alveolar–arterial ($A\text{-}aO_2$) gradient (pH: 7.47, partial pressure of carbon dioxide 27 mm Hg, partial pressure of oxygen 68 mm Hg, $A\text{-}aO_2$ gradient 45.6). Electrocardiogram showed nonspecific changes. Echo showed no chamber enlargement with systolic ejection fraction of 60%, mild tricuspid regurgitation, and no evidence of right ventricular dysfunction. Screening for DVT with compression ultrasonography, Doppler study of bilateral lower limb veins, bilateral iliac veins and inferior vena cava did not show evidence of thrombosis (Fig. 1). Since the patient had intermediate clinical probability of PE based on modified Wells scoring and revised Geneva scoring, D-dimer levels were determined which were

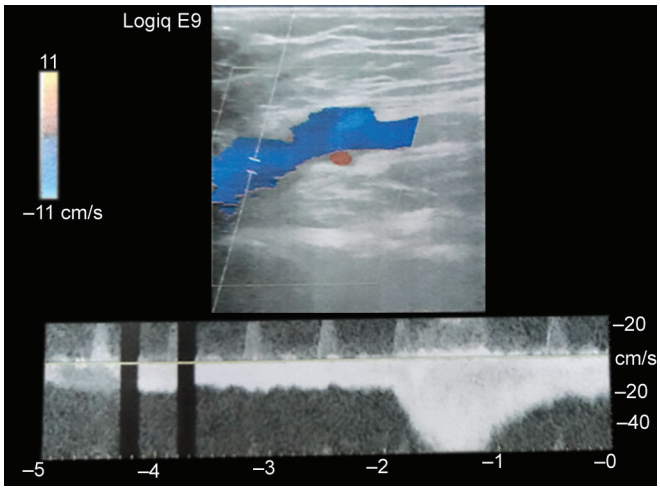

Fig. 1: Doppler ultrasonogram of deep veins of leg and pelvis showing normal filling

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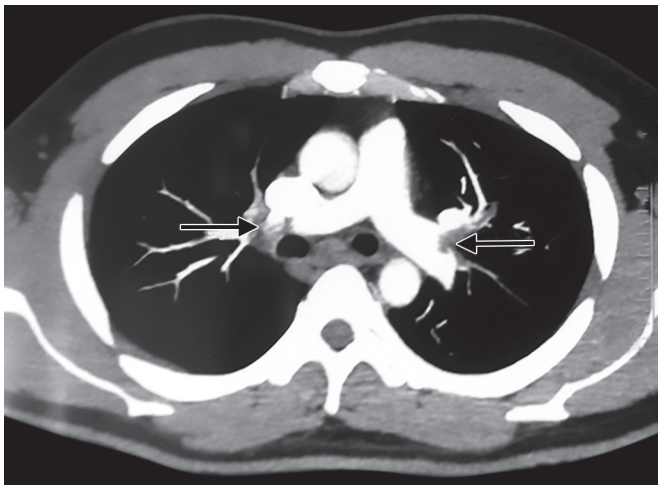

Fig. 2: The CT pulmonary angiogram showing evidence of embolism in bilateral pulmonary artery (arrowheads)

raised. Computed tomography (CT) pulmonary angiogram done revealed acute pulmonary thromboembolism involving right and left main pulmonary artery with extension to right superior lobar branch and left superior and inferior lobar branches (Fig. 2). Cardiac enzyme markers Troponin I and B-type natriuretic peptide were normal. Risk stratification with pulmonary embolism severity index (PESI) score categorized patient to intermediate–low-risk group and patient was treated conservatively with parenteral anticoagulation. Evaluation for prothrombotic condition with protein C, protein S, antithrombin, Factor 5 Leiden mutation, and hyperhomocysteinemia was negative. Since the etiology was inconclusive and prior studies had considered OSA as a risk factor for PE, polysomnography (PSG) was done in the patient. The PSG showed multiple episodes of apnea, hypopnea, and respiratory effort-related arousals with significant nocturnal desaturation, suggesting OSA (Fig. 3). Continuous positive airway pressure (CPAP) titration at 9 cm H_2O abolished all events including snoring. After 10 days of therapeutic parenteral anticoagulation with enoxaparin, patient was administered novel anticoagulant, dabigartan 150 mg twice daily along with CPAP support and oxygen supplementation, and was discharged. Currently, our patient is on extended anticoagulation and has symptomatic improvement without any recurrence.

DISCUSSION

Pulmonary embolism, a major manifestation of VTE, has an annual incidence of 1 to 2 cases per 1000 person years and is associated with significant morbidity and mortality.[1] Data from various cross-sectional and longitudinal studies indicate that OSA may be an independent risk factor for VTE diseases and both share common risk factors of advanced age, physical inactivity, and obesity.[2] Studies have also observed an increased recurrence of PE in patients of OSA and for every 10-unit rise in apnea–hypopnea index, the risk of PE increases by 45%.[3] This is of major concern due to the high prevalence of OSA and high morbidity and mortality associated with PE.

It is observed that patients with OSA have hypercoagulable state characterized by elevated platelet activity, fibrinogen levels, plasminogen activator inhibitor-1 levels, polycythemia, erythrocyte adhesiveness, and aggregation.[4-6] Vascular endothelial injury due to recurrent hypoxia and reoxygenation and venous stasis due to physical inactivity and secondary polycythemia in OSA promote VTE.[7] In the present case, the patient had normal body mass index and no other identifiable risk factors of trauma, major surgery, prolonged immobilization, varicose vein, malignancy, obesity, chronic obstructive lung disease, long-distance travel in sitting

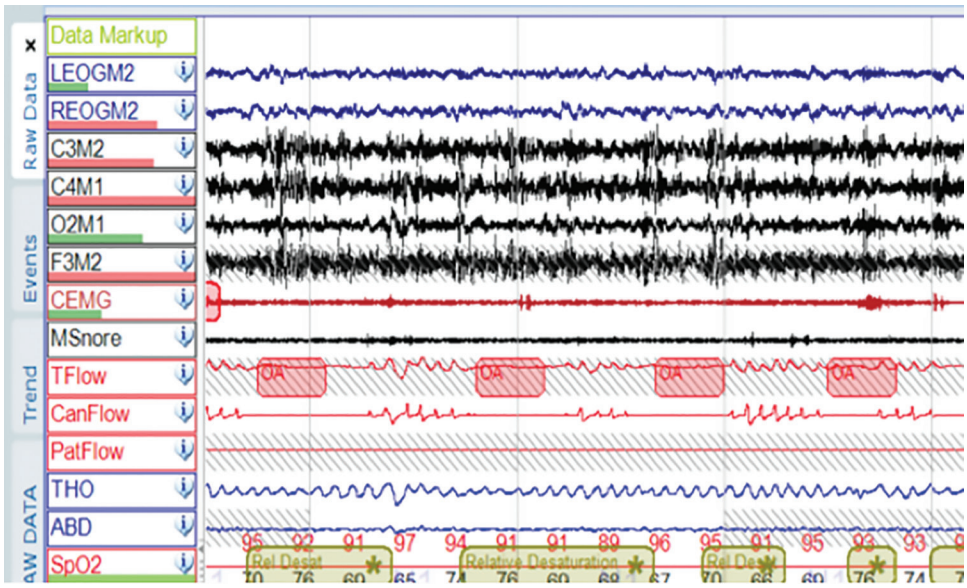

Fig. 3: Epoch from PSG showing findings of OSA

posture. We also excluded other hypercoagulability causes of unprovoked PE like deficiency of protein C, protein S, antithrombin 3, Factor 5 Leiden mutation and hyperhomocysteinemia, suggesting that OSA could be the etiology of PE in our patient. The polycythemia in this patient can be attributed to nocturnal hypoxemia due to OSA and this may have promoted venous stasis. *De novo* formation of clots within the pulmonary artery or *in situ* thrombosis due to localized inflammation, endothelial cell damage in OSA may be the reason for the presence of isolated PE in the absence of DVT in our patient.[8] This presentation deserves mention, as these patients would likely not benefit from vena caval filters in case of recurrence.

In accordance with the 2014 guidelines of PE,[9] "advanced" risk assessment PESI score was done. Patient was in intermediate–low-risk group as the RV function was normal on echocardiography and CT angiography, and the patient had normal cardiac biomarker levels. The CPAP was observed to reduce apnea-hypopnea index, hypercoagulation, clot strength and clotting index in patients with concomitant sleep apnea and VTE.[10] However, the contribution of CPAP in secondary prophylaxis of thrombotic events is uncertain. In the present case, patient was hospitalized and received parenteral anticoagulation for 10 days followed by oral dabigatran as extended secondary prophylaxis was deemed. Patient was also initiated on CPAP at 9 cm H_2O to eliminate all obstructive events.

The OSA increases the risk of recurrent PE and other thromboembolic events. Studies have observed that an elevated D-dimer level after stopping anticoagulation is associated with a higher recurrence rate;[11] however, the utility of serial monitoring and re-initiation of anticoagulation remains debatable. Addition of sleep indices like apnea–hypopnea index, mean nocturnal oxygen saturation (SaO_2), and the percentage of total time study spent with $SaO_2 < 90\%$ to disabilities of the arm shoulder and Hand symptom score,[12] and Vienna prediction model[13] may improve risk assessment of recurrent PE.

Current guidelines recommend at least 3 months of treatment after initiation of warfarin/novel anticoagulant for PE and DVT.[9] The aim of continuing anticoagulation beyond 6 months is to prevent recurrent thrombosis (prophylaxis).[14] Though it is believed that extended anticoagulation beyond 6 months is required in these patients, there are no randomized controlled trials to verify if these patients can really benefit from prolonged duration anticoagulant treatment. Currently, our patient is on extended anticoagulation and has symptomatic improvement without any recurrence. Such patients should be followed up regularly, as these patients may have recurrence or may progress to chronic thrombopulmonary embolism.

CONCLUSION

The OSA should be evaluated for all patients with unidentifiable cause of PE and in recurrent PE. These patients should be treated with adequate positive airway pressure therapy and prolonged duration of anticoagulation.

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