PET/CT showed bilateral hypermetabolic pneumonic pulmonary opacities and confirmed a moderate amount of right PE (Fig. 1C). Serosanguineous pleural fluid with the following characteristics was obtained: pH 7.43, glucose 104 mg/dl (serum glucose 91 mg/dl), lactate 3.2 mmol/l, pleural fluid protein/serum protein ratio: 0.70, pleural fluid LDH/serum LDH ratio: 2.37, LDH pleural fluid: 524, hematocrit <15%, lymphocytes 28.7%, neutrophils 0.0% (criteria for lymphocytic exudate) and negative microbiological tests, thus ruling out PE due to infection. Flow cytometry of pleural fluid detected 60% large neoplastic plasma cells (plasmablasts), CD 138+ and CD 56−, which confirmed the malignant nature of the PE (myelomatous). Jugal mucosa biopsy ruled out the presence of amyloid deposits. The patient was initially treated with antibiotics (piperacillin–tazobactam) and subsequently underwent right pleural drainage followed by chemical pleurodesis with talc, local radiotherapy and chemotherapy (pomalidomide–dexamethasone–cyclophosphamide), presenting excellent clinical and radiological progress (Fig. 1D).

During the course of MM, 15%–30% of patients may develop extramedullary involvement.[1] The pleural cavity is an unusual site for MM recurrence; in fact, MPE occurs in only in 1% of cases of PE in patients with MM. In a recently published series, MPE represented only 0.6% of malignant PEs.[2,3] Diagnostic criteria for MPE are: (1) presence of atypical plasma cells in pleural fluid (neoplastic plasma cells or a monoclonal component); (2) pleural biopsy consistent with neoplastic plasma cells, or (3) demonstration of monoclonal proteins in the pleural fluid by electrophoresis. In doubtful cases, flow cytometry helps establish the immunophenotype of neoplastic plasma cells compared to that of reactive cells. When a patient with MM develops PE, it is important to rule out common etiologies, such as paraneumonic PE, heart failure, kidney failure, and amyloidosis. The latter may cause PE due to cardiac (heart failure), renal (nephrotic syndrome), liver (ascites), or pleuropulmonary involvement.[4] MPE can be caused by an abnormal proliferation of plasma cells from an extramedullary plasmacytoma of the chest wall, invasion from an adjacent bone lesion, or direct invasion of the pleura by myeloma.[5] While various treatments are available for MPE (chemotherapy, therapeutic thoracentesis, chest drain, or pleurodesis), there is no consensus about how we should manage these patients. Extramedullary involvement is associated with an adverse prognosis, especially when it is recurrent MM. Pleural infiltration is usually fatal, with a median survival of 1.5–3 months. Therefore, more aggressive chemotherapy regimens can be indicated in MM with involvement of the pleural cavities. Our patient responded well to multimodal treatment consisting of a combination of radiation therapy, chemotherapy, and chemical pleurodesis, achieving clinical remission that lasted 6 months after diagnosis of the MPE.

This case reminds us that we must investigate all the causes of PE in patients with a history of MM and that, although the incidence of MPE is low, it must be taken into account as a diagnostic possibility. Its grim prognosis and aggressive natural course require us to make a quick and appropriate diagnosis in order to start treatment as soon as possible.

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Overnight Change in Urinary Prostacyclin and Thromboxane in Obstructive Sleep Apnea

Cambio en la prostaciclina y el tromboxano urinario durante la noche en la apnea obstructiva del sueño

Dear Editor,

Obstructive sleep apnea (OSA) is a common disorder[1] eliciting sympathetic alterations and intermittent hypoxia (IH) resulting in oxidative stress and inflammation. As a result, OSA has been linked to enhanced cardiovascular (CV) disorders and hypercoagulability,[2] endothelial function, intima-media thickness, and high blood pressure.[3]

Prostanoids (PG) are products of arachidonic acid catabolism by cyclooxygenase (COX) isoenzymes COX-1 and COX-2. Among PG, Thromboxane (TXA_2) and Prostacyclin (PGI_2) are known for their role as regulators of vascular tone, remodeling and angiogenesis. TXA_2 is mainly generated by platelets through COX-1 and quickly metabolized into Thromboxane B2 (TXB_2). TXA_2 induces platelet activation, vasoconstriction, and vascular smooth muscle cell proliferation. On the other hand, PGI_2 mostly depends on endothelial COX-2 and prostacyclin synthase enzymes. PGI_2 is metabolized into 6-keto Prostaglandin $F_{1\alpha}$ (6-ketoPGF$_{1\alpha}$). PGI_2 inhibits platelet aggregation and vasoconstriction. Therefore, TXA_2 and PGI_2 have antagonist properties and are both excreted in urine and plasma.[4] Aspirin (acetyl salicylic acid, ASA) is a non-selective COX inhibitor with beneficial anti-thrombotic effects by inhibiting the release of TXA_2. Although ASA can also inhibit the synthesis of PGI_2 which has anti-thrombotic effect, more pronounced inhibition of TXA_2 versus PGI_2 has been detected in humans after low-dose ASA.[4]

Recently, our group reported that pre-atherosclerotic aorta remodeling induced by chronic IH mimicking OSA in mice can be prevented by ASA treatment.[5] We here hypothesize, that ASA preventive effects are related to its capacity to inhibit COX-1 and COX-2 pathways. Thus, the aim of the present study is to characterize TXA_2 and PGI_2 overnight change according to OSA severity, and to investigate the effect of ASA treatment in this overnight change.

We conducted an observational pilot study approved by the Hospital Clinic Ethics Board including 52 patients with OSA suspicion consecutively referred to our sleep laboratory. Either polysomnography or respiratory polygraph was used for diagnosis. All studies were analyzed following the AASM rules[6] and divided by apnea-hypopnea index (AHI) severity (low ≤30 events/h and high >30 events/h) and ASA prescribed as regular medication: low AHI group ($n=27$): 5/27 with ASA; and high AHI group ($n=25$): 10/25 with ASA. Patients on other nonsteroidal anti-inflammatory treatments were excluded. Patients data were: 73.1% male, 58.0 ± 12.3 yr old, body mass index (BMI) 28.9 ± 4.6 kg/m^2, apnea hypopnea index (AHI) 29.9 ± 20.5 events//h, oxygen desaturation index 3% (ODI3%), 26.0 ± 20.2 events/h.

To assess overnight changes in PG metabolites, urine samples were collected right before patients went to sleep (night) and just after awakening (morning), and immediately stored at −80 °C. Subsequently, PG determinations were conducted using Elisa kits for: 11-dehydro Thromboxane B2 (TXB_2) and 6-keto-prostaglandin $F_{1\alpha}$ (6-ketoPGF$_{1\alpha}$) (Cayman Chemical, Ann Arbor, Michigan, USA). Variables across groups were compared with Wilcoxon matched-pairs signed-ranks test and Wilcoxon-Mann–Whitney test. Significance level was set at $p=0.05$.

From a total of 52 patients, PG values were measured at the beginning and at the end of the night, in order to evaluate overnight changes according to AHI groups and ASA prescription (Fig. 1). Urinary 6-keto-PGF$_{1\alpha}$ night values were higher in the high AHI than in the low AHI group, but surprisingly they significantly decreased overnight in patients with high AHI levels ($n=25$; $p=0.006$) and no-ASA treatment ($n=15/25$; $p=0.006$), while in patients on ASA treatment ($n=10/25$), 6-keto-PGF$_{1\alpha}$ levels drop was not significant. On the other hand, TXB_2 increased overnight on both AHI groups, but only significantly in the low AHI group ($n=27$; $p=0.015$). As expected, TXB_2 was lower in all ASA-treated patients ($n=15$) and non-significant overnight changes were related to ASA. 6-keto-PGF$_{1\alpha}$/TXB_2 ratio was significantly decreased overnight in both AHI groups ($p<0.05$), with no differences between AHI severity groups. 6-keto-PGF$_{1\alpha}$/TXB_2 ratio drop remained significant in patients with high AHI and no-ASA treatment ($n=15/25$; $p=0.008$). A regression model resulted in similar findings when adjusting by age, gender and BMI.

Our study demonstrated that in severe OSA patients there is a significant overnight drop of PGI_2 metabolite (6-keto-PGF$_{1\alpha}$) in comparison to patients with lower AHI. Meanwhile, TXB_2 increased in both groups and resulted in a 6-keto-PGF1α/TXB_2 decreased ratio. The results previously reported in the literature were controversial. In accordance with our findings, urinary excretion of PG metabolites in OSA patients suggested a decreased production of dilatory (PGI_2) versus constrictor PG (TXB_2) expressed by a decreased PGI_2/TXB_2 ratio.[7] Nevertheless, Kimura et al. found a compensatory increase in dilatory PG.[8] And more recently Mejza et al. observed that 6-keto-PGF$_{1\alpha}$ urine and serum concentrations were significantly higher in OSA patients when compared to controls.[9] Though, TXB_2 levels in urine and serum were not significantly different between groups,[8] concurrently with our sample. Beaudin et al. assessed IH acute effect in healthy patients ($n=12$) mimicking severe OSA and PG were unaffected, but these authors found elevated TXA2 levels between in OSA patients compared to the healthy basal levels.[10] However, these results must be regarded with caution due to the very small number of patients included in those studies.[7–10]

Therefore, considering the activation of the TXA_2-pathway in OSA patients, particularly with CV comorbidities[11] and taking onto account CPAP failure to reduce CV risk[12] and TXA_2 metabolites excretion,[11] we suggest that targeting the COX-1-pathway could represent an alternative strategy to prevent or delay the deleterious CV consequences linked to OSA.[13] Yet, in our study regular treatment with ASA had no significant effect over overnight TBX_2 increase, probably because the TBX2-pathway was already under ASA inhibition and the limitations of a small sample of patients treated with ASA ($n=15$). Discrepancies between clinical studies and our murine model[5] could also be explained by the greater severity of IH in animal models compared to OSA patients and other contributing factors such as BMI and comorbidities in patients.[13] Since this was not an interventional study, the patients ASA treatment could be associated to CV comorbidities or risk factors. Surprisingly, the present study shows that the expected up-regulation of the COX-2 pathway resulting in an increase in the release of protective PGI_2 does not take place during the repetitive overnight episodes of hypoxia in OSA patients. Whether this apparent anomaly contributes to the deleterious CV effects of OSA remains to be clarified.

Although the limited number of patients in this pilot study does not allow us to derive solid conclusions with regards to clinical practice, it provides a proof of concept suggesting the interest of further research in larger samples, since it could open new approaches for OSA-CV risk management.

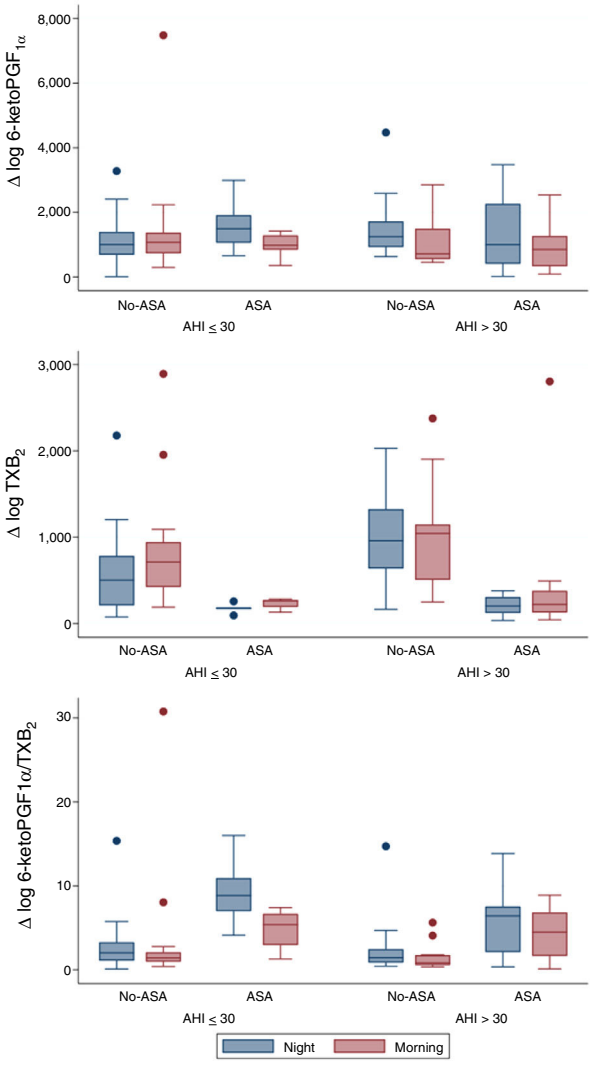

Fig. 1. 6-keto-PGF$_{1\alpha}$, TXB_2 and 6-keto-PGF$_{1\alpha}$/TXB_2 overnight changes according to AHI severity and ASA treatment (Box plot).

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An Unusual Combination of Diffuse Pulmonary Cysts and a Nodule

Una combinación infrecuente de quistes pulmonares difusos y un nódulo

Dear Editor:

A 59-year-old asymptomatic woman was referred to our outpatient clinic to investigate a diffuse cystic lung disease (DCLD) incidentally found on abdominal computed tomography (CT). Her past medical history revealed obstructive sleep apnea and Paget disease, for which she used zoledronic acid. She denied smoking and had no relevant exposure. Physical examination was normal and her peripheral oxygen saturation was 98% on room air. Chest high-resolution CT (HRCT) revealed multiple thin-walled pulmonary cysts diffusely distributed in both lungs and a 10 mm ground-glass nodule in the right upper lobe (Fig. 1). Pulmonary function tests (PFTs) showed normal spirometry, air trapping (RV, 166% of predicted; RV/TLC ratio, 0.51) and a mild reduction in DLCO (60% of predicted). Serum markers of inflammatory activity, protein electrophoresis, alpha 1 antitrypsin serum dosage were normal, and antinuclear antibodies, rheumatoid factor, anti-Ro/SSA and anti-La/SSB were negative. The serum level of vascular endothelial growth factor-D was 407 pg/mL and abdominal ultrasound and scintigraphy of salivary glands were normal. She refused to undergo a surgical lung biopsy for diagnostic elucidation. The nodule remained stable during the follow-up.

After 5 years of follow-up, PFTs were stable and there was an increase in the nodule size (13 mm), with a solid composition (Fig. 1). There was a mild increase of glycolytic metabolism (SUV 2.6) on the combined positron emission tomography/CT. There was no evidence of lymph node enlargement or extrapulmonary disease. A right upper lobectomy with lymphadenectomy was performed after an adenocarcinoma has been confirmed in the intraoperative frozen section. Histopathological analysis revealed a predominantly acinar invasive adenocarcinoma, with lepidic and micropapillary components, which was classified as Stage IA (T1aN0M0). The lung parenchyma around the tumor revealed a heterogeneous small airway disease characterized by variable narrowing of the small airways, abnormal bronchioles with subepithelial fibrosis and scattered chronic inflammatory cells, associated with peribronchiolar alveolar overdistension, which was consistent with constrictive bronchiolitis (Fig. 1).

The differential diagnosis of DCLD is broad and establishing a definite diagnosis may be challenging. Although chest HRCT has substantially contributed to the approach of DCLD, lung biopsy may be necessary to confirm the etiology.[1,2] Constrictive bronchiolitis is rarely included in the differential diagnosis of DCLD, but it is a potential etiology.[1,2] The proposed physiopathology involved is a bronchiolar check-valve mechanism, with air trapping and distension of distal airspace resulting in cysts formation.[3] Our case