138+ y CD 56−, que confirmó la naturaleza maligna (mielomatosa) del DP. Una biopsia de mucosa yugal descartó la presencia de depósitos amiloideos. El paciente en un principio fue tratado con antibióticos (piperacilina-tazobactam) y posteriormente se realizó drenaje pleural derecho seguido de pleurodesis química con talco, radioterapia local y quimioterapia (pomalidomida-dexametasona-ciclofosfamida), presentando una excelente evolución clínica y radiológica (fig. 1D).

Durante el curso del MM, del 15 al 30% de los pacientes pueden llegar a desarrollar una afectación extramedular[1]. La cavidad pleural es una localización inusual para la recurrencia de MM; de hecho, el DPM está presente únicamente en el 1% de los casos de DP en pacientes con MM. En una serie recientemente publicada, el DPM representó tan solo el 0,6% de los DP malignos[2,3]. Los criterios diagnósticos del DPM son: 1) presencia de células plasmáticas atípicas en el líquido pleural (células plasmáticas tumorales o de un componente monoclonal); 2) biopsia pleural compatible con células plasmáticas malignas, o 3) demostración de proteínas monoclonales en el líquido pleural mediante electroforesis. En casos dudosos, la citometría de flujo ayuda a filiar el inmunofenotipo de las células plasmáticas neoplásicas en contraposición con el de las células reactivas. Cuando un paciente con MM desarrolla un DP es importante descartar etiologías comunes en estos pacientes, como son el DP paraneumónico, la insuficiencia cardiaca, la insuficiencia renal o la amiloidosis. Esta última puede provocar DP por la afectación cardíaca (insuficiencia cardiaca), renal (síndrome nefrótico), hepática (ascitis) o pleuropulmonar[4]. El DPM puede ser secundario a una proliferación anormal de células plasmáticas de un plasmocitoma extramedular de la pared torácica, invasión desde una lesión ósea adyacente o invasión directa pleural por mieloma[5]. Aunque se dispone de diversos tratamientos para el DPM (quimioterapia, toracocentesis terapéuticas, colocación de drenaje torácico o pleurodesis), no existe consenso sobre cómo se deben manejar estos pacientes. La afectación extramedular se asocia a un pronóstico adverso, especialmente cuando forma parte de una recurrencia del MM. La infiltración pleural resulta generalmente fatal, con una mediana de supervivencia de 1,5-3 meses. Por lo tanto, en el MM con afectación de las cavidades pleurales se pueden indicar los regímenes de quimioterapia más agresivos. Nuestro paciente ha respondido bien a un tratamiento multimodal en el que se han combinado radioterapia, quimioterapia y pleurodesis química, lográndose una remisión clínica que perdura 6 meses después del diagnóstico del DPM.

Este caso nos recuerda que debemos investigar todas las causas de DP en pacientes con antecedentes de MM y que, aunque los DPM tienen una baja incidencia, deben tenerse en cuenta como posibilidad diagnóstica. Su pronóstico ominoso y el curso natural agresivo nos obliga a realizar un diagnóstico rápido y adecuado para iniciar un tratamiento lo antes posible.

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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

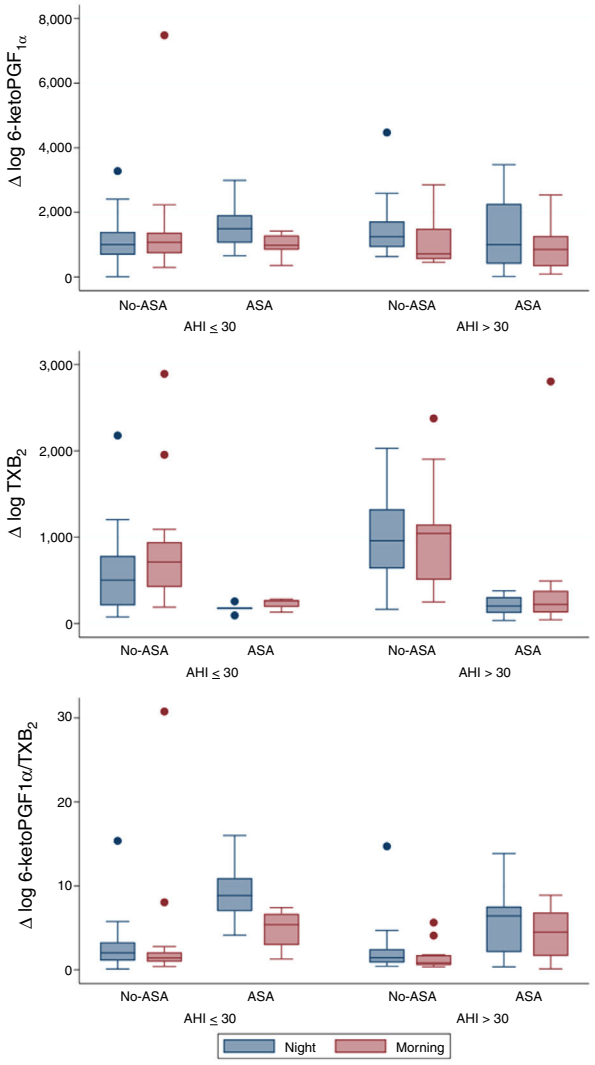

Fig. 1. 6-keto-$PGF_{1\alpha}$, TXB_2 and 6-keto-$PGF_{1\alpha}$/TXB_2 overnight changes according to AHI severity and ASA treatment (Box plot).

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-keto$PGF_{1\alpha}$) (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.

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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 corroborates such hypothesis, supported by the finding of downstream hyperdistension of distal airways and alveolar spaces.

One may also speculate about the relationship between the small airway disease and the incidental lung cancer. The initially