y eosinofilia periférica (4.128 cél/mm^3), con ANCA negativo y buena respuesta a meprednisona. En 2013 fue hospitalizada por fiebre, infiltrados pulmonares, miocarditis y derrame pericárdico. Se sospechó GEPA y fue medicada con meprednisona y azatioprina. La paciente continuaba con mal control del asma, eosinofilia periférica, defecto obstructivo moderado en espirometría y leve reducción de la capacidad de difusión. En mayo de 2018 inició tratamiento con mepolizumab 100 mg/mes, presentado mejoría sostenida clínica y funcional.

Mujer de 49 años con antecedente de rinosinusitis crónica y asma bronquial. En 2010 (a los 40 años de edad) fue controlada por fiebre y disnea, presentó infiltrados pulmonares alvéolointersticiales difusos, eosinofília periférica (1.802 eosinófilos), IgE elevada, con p-ANCA MPO positivo. Se diagnosticó GEPA y se medicó con meprednisona, con recaída al suspender esteroides sistémicos. Fue tratada secuencialmente con esteroides más azatioprina por 2 años, omalizumab durante un año y rituximab un año. La paciente continuó sintomática por lo que se inició tratamiento con mepolizumab 100 mg/mes en septiembre de 2018. Presentó pronta y sostenida mejoría clínica y funcional respiratoria.

La GEPA es una vasculitis sistémica que compromete pequeños y medianos vasos, se asocia a asma en general de difícil control. Requiere tratamiento de inducción y mantenimiento con esteroides e inmunomoduladores, con frecuentes recaídas y potenciales efectos adversos graves. El anti-IL-5, mepolizumab, ha sido evaluado recientemente como una nueva alternativa terapéutica con resultados promisorios. En el ensayo de Wechsler et al.[5], mepolizumab fue administrado a dosis de 300 mg por vía subcutánea cada 4 semanas y se asoció con una menor frecuencia de recaídas y mayor tiempo acumulado en la remisión de la enfermedad que en el grupo placebo, permitiendo reducciones en la dosis de glucocorticoides.

El único estudio randomizado, placebo controlado publicado[5] utilizó dosis de mepolizumab de 300 mg/mes en pacientes con GEPA, sin evaluar el efecto de dosis inferiores, no encontrando referencias que justifiquen esta dosis. Pouliquen et al.[10] evaluaron la respuesta de los eosinófilos en sangre a dosis creciente de mepolizumab, evidenciando una inhibición máxima del 90% de los eosinófilos periféricos a las 12 semanas con dosis subcutánea de mepolizumab de 99 mg.

Los 3 pacientes presentados fueron tratados con dosis subcutánea de 100 mg/mes logrando disminución en el conteo de eosinófilos periféricos, con mejoría de las manifestaciones pulmonares y extrapulmonares, y permitiendo la retirada de esteroides sistémicos. Estos pacientes mantuvieron en su seguimiento la mejoría, no presentaron recaídas y no requirieron incremento de dosis.

Nuestra publicación es limitada en el número de pacientes, pero abre la posibilidad de utilizar inicialmente dosis menores de mepolizumab en pacientes con GEPA.

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https://doi.org/10.1016/j.arbres.2019.09.019

Addition of Rituximab to Oral Corticosteroids in the Treatment of Chronic Hypersensitivity Pneumonitis

Adición de rituximab a los corticosteroides orales en el tratamiento de la neumonitis por hipersensibilidad crónica

Dear Editor,

Chronic hypersensitivity pneumonitis (CHP) is an entity characterized by a destructuring of the lung parenchyma as a result of an inflammation of immunological origin, secondary to the repeated inhalation of an antigen (usually of an organic nature) to which the individual has previously been sensitized.[1] In early stages, antigen avoidance can contribute to the resolution of the disease; however, in chronic stages the evolution usually progresses despite antigen avoidance and treatment with systemic corticosteroids, with a 5-year mortality rate of 31%.[2,3]

Rituximab is a pan-B murine/human chimeric monoclonal antibody which binds specifically to the CD20 membrane antigen and has been used successfully in some interstitial lung diseases (ILDs) associated with collagen diseases.[4,5] A case has been described in which rituximab was shown to be effective in the treatment of CHP, obtaining a significant symptomatic improvement with increases of 40% in the CO transfer test (DLCO) and of 15% in the forced vital capacity (FVC).[6] In another series of six patients with CHP, functional stability was also observed in three.[7]

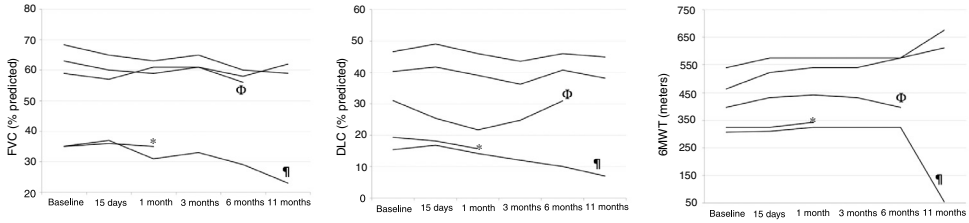

Fig. 1. (A) Evolution of the forced vital capacity; (B) evolution of the CO transfer test; (C) evolution of the 6-minute walking distance. *Acronyms*: FVC, forced vital capacity; DLCO, CO transfer test; 6MWT, 6-minute walking test; *, the patient died at month 3 of follow up; ¶, the patient died at month 11 of follow up; Φ, one patient was unable to perform FVC, DLCO and 6MWT at month 11 due to a high respiratory tract infection.

The objective of the present study was to describe the effect of rituximab in a series of five patients with CHP, who presented a progressive loss of pulmonary function despite conventional treatment with systemic corticosteroids and avoidance of contact with the causative antigen.

Five patients diagnosed with CHP who had presented decreases in FVC of more than 10% and/or in DLCO of more than 20% over the previous two years were treated with two doses of 1000 mg of rituximab, administered intravenously, separated by an interval of 15 days. This retrospective review describes our experience with these five CHP patients with poor evolution despite conventional treatment, who were treated compassionately with rituximab in accordance with current clinical practice.

The study was authorized by the Ethics Committee of the local hospital. The five patients gave their informed consent to participate.

CHP was diagnosed in accordance with the criteria of Schuyler et al.,[8] and patients also fulfilled the currently accepted criteria proposed by Vasakova et al.[9] The FVC, DLCO and the 6-minute walking distance (6MWD) were measured at baseline, at 15 days and at 1, 3, 6 and 11 months. A chest high resolution computed tomography (HRCT) was performed at baseline, at 20 days (in order to discard drug toxicity), at 3 months and 11 months after treatment, with assessment of the profusion and/or the appearance of new images.

The median age of patients was 72 years (p25–p75 72–73). All patients were male, and four of the five were ex-smokers (>10 packsq/year). They initially had a median FVC of 59% and a median DLCO of 31%, and in the 6MWD they had walked a median of 396 m (324–463 m). As regards the HRCT, all the patients presented peribronchovascular fibrosis, traction bronchiectasis, mosaic attenuation, air trapping and relative sparing of the bases. Ground glass opacities were minimal or absent in all patients.

Eleven months after the treatment with rituximab, patients had median decreases of 9.3% (−11.8 to 3.2) in FVC and of 2.2% (−8.4 to −1.7) in DLCO (Fig. 1), and median increases of 72 m (−252 to 213 m) in 6MWD. There were no significant changes in the HRCT images in any of the patients, at 20 days at 3 months or at 11 months (Fig. 1).

Two patients died during follow-up; one of them in the third month, and the other, eleven months after rituximab administration. In both cases, death was attributed to progression of the underlying disease. No adverse effects were observed related to the administration of rituximab.

The three patients with an initial FVC greater than 50% and a DLCO greater than 30% did not present significant reductions in these two values during the study period. These three patients raised their 6MWD up to the limit of significance ($p < 0.06$) despite the small sample size. These results seem promising, bearing in mind that both 6MWD and change in 6MWD have been shown to be independent predictors of mortality in other fibrotic ILDs.[10]

The two patients who presented very low pulmonary function values at the time of treatment (FVC 35% and 34.5%, and DLCO 18% and 15% respectively) were both exitus, at months 3 and 11 of follow-up respectively. In these patients, rituximab did not improve or stop the fall in FVC and DLCO, nor did it improve the distance covered in the 6MWD.

Interestingly, the three patients who presented FVC values of 50% or more and DLCO values of 30% or more at baseline presented an almost significant benefit in the 6MWD, and a stabilization of the lung function values during follow-up after treatment with two doses of rituximab. This suggests that, in early phases of the disease, the addition of rituximab may to some extent help to stabilize the disease. Although it has traditionally been considered that the inflammation in HP is predominantly mediated by T lymphocytes, self-reactive B lymphocytes with the mediation of T lymphocytes may play a decisive role in this inflammatory chain, which would suggest a possible favourable effect of treatment with rituximab in the initial phases of CHP.[11]

No infectious complications (opportunistic infections, fungal infections or isolation of mycobacteria) were identified related to the administration of rituximab. These data coincide with other studies of patients with ILDs treated with rituximab, and confirm the relative safety of the use of the drug in this subgroup of patients, although close monitoring is mandatory.

The small number of patients and the absence of a control group mean that no definitive conclusions can be obtained. However, the favourable evolution presented by other sporadic cases[6,7] and by the patients described here suggests that rituximab may be of some utility in a subgroup of patients with CHP who do not respond to antigen avoidance and treatment with systemic corticosteroids. Randomized controlled clinical trials should be carried out in order to confirm these encouraging initial findings.

Funding

Beca *Fundacio Catalana de Pneumologia* (FUCAP) and Fundación Cellex.

Conflicts of interest

The pharmaceutical industry did not participate in the conception, nor in the financing of the study. IO has received consulting fees, talk fees or research grants from Astrazeneca, Boehringer Ingelheim, GlaxoSmithKline, Mundipharma, Novartis and TEVA. AV has received consulting fees, talk fees or research grants from Boehringer Ingelheim, GlaxoSmithKline and Roche. XM has received consulting fees, talk fees or research grants from AstraZeneca, Boehringer Ingelheim, Chiesi, Faes, GlaxoSmithKline, Menarini, Mundifarma, Novartis and Teva.

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https://doi.org/10.1016/j.arbres.2019.07.013

Allergic Bronchopulmonary Aspergillosis With Elevated CEA Is Infrequent

La aspergilosis broncopulmonar alérgica con niveles elevados de antígeno carcinoembrionario (CEA) es infrecuente

Dear Editor:

Allergic bronchopulmonary aspergillosis (ABPA) is a complex hypersensitivity reaction in response to colonization of the airways with *Aspergillus fumigatus*.[1] It occurs primarily in patients with asthma or cystic fibrosis (CF).[2,3] We report a case of this disease without asthma or CF, but with an elevated carcinoembryonic antigen (CEA) instead.

A 46-year-old woman, non-smoker, with no history of asthma or recurrent lung disease was admitted to the hospital for paroxysmal cough for two months. She denied expectoration, shortness of breath, chest pain, hemoptysis, fevers or chills. During the course of her illness, the patient lost 2.5 kg of weight with poor appetite. She has a surgical history of lingular segment of the left upper pulmonary lobe resection in 2015, and the histopathological report showed bronchiectasis, acute infections and abscesses. Laboratory data revealed a markedly elevated blood eosinophil count and percentage (1.2×10^9/L, 15.1%) and total serum level of immunoglobulin E (1412 kU/L). Chest CT revealed shadow in the medial basal segment of the right lower lobe and the upper left lung, right lung bronchiectasis and infection on 11th January 2018 (Fig. 1). In considering of her surgical history and chest CT, we tested several tumor markers to rule out primary and metastatic tumors. The serum CEA (24.2 ng/mL) was remarkable elevated, while serum CA19-9 level was normal. A subsequent PET scan showed no focal increase in fluorodeoxyglucose activity. Bronchoscopy showed inflamed bronchial mucosa and cytological examination of bronchoalveolar lavage fluid showed no cancer cells nor heterotypic cells. Pulmonary function test results showed a vital capacity of 2.87 L (75.3% of predicted), FVC of 4.14 L (80% of predicted), FEV1 of 2.15 L (84.5% of predicted), FEV1/FVC ratio of 74.86%. According to the patient's pulmonary function at that time, when the cumulative dose of acetylmethcholine reached 2.5 mg (12.8 micromole), FEV1 decreased by 11.0% in the patient. Bronchial histamine provocation test and bronchodilator test were negative. She was limited response to levofloxacin treatment. Subsequently, the results of *A. fumigatus*-specific IgE 8.26 kUA/L, *A. fumigatus*-specific IgG > 500 AU/mL. One month oral corticosteroid treatment was helpful for improving patient's symptom and radiological abnormality (Fig. 1). Total IgE concentration, which is a key indicator for assessing the treatment response and relapse, was rapidly declined after 3 months treatment associated with symptomatic improvement. The concentration of serum CEA decreased to normal range 6 months later. No relapse has been observed throughout the one-year follow-up (Table 1).

CEA, is known to be one of the most extensively used clinical marker for colorectal carcinoma and lung cancer.[4] It can be produced in the epithelium of the stomach, intestines, bile ducts, and respiratory tract ranging from the trachea to the alveoli and plays a role in the progress of cell adhesion and participate in the innate immune defense.[5] Noguchi et al. measured serum CEA levels in patients with ABPA and found serum CEA levels are elevated in some patients with ABPA, which might be associated with consolidation in the lung.[6] Elevated serum CEA levels decrease as the consolidation decreases after treatment. The elevation of serum CEA might be attributed to the presence of local inflammation in the lung. We found several cases reported asthmatic patients with high level of CEA in serum and bronchoalveolar lavage fluid might be related to the mucoid impaction.[7,8] In our case, we found the level of CEA was not directly related to the mucoid impaction in our follow-up. Tang et al. have discovered that the increase level of CEA was related to the increase number of eosinophil granulocytes, and corticosteroid therapy was effective in improving clinical symptoms and the CEA values decreased in association with the improvement of those manifestations, suggesting a pathophysiological link between the disease activity of hypereosinophilia and the changes in CEA level.[9,10] In our case, we found that the level of CEA decreased along with the decrease of eosinophil granulocytes. The underlying mechanism remains unclear. Besides, there is also a report showing that a 21-year-old man with bronchial asthma who suffered from productive cough had an elevated serum CA19-9 level.[11] In that case, immunohistochemical studies showed no expression of CA19-9 in bronchial biopsy specimens, but the CA19-9 level recovered to normal range after steroid therapy. This indicates that the high serum concentration of CA19-9 was probably due to hypersecretion of mucus glycoprotein, secreted from hypertrophic glands or/and epithelial cells in the bronchioles. These finding suggests that CEA is correlated with the inflammatory activity of ABPA while