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A New Clinical Scenario: the Presence of Neutrophil Anti-Cytoplasm Antibodies in the Combination of Pulmonary Fibrosis and Emphysema (CFPE)

Jose Salvador García-Morillo*, David Blanco Alba and Santiago Rodríguez Suárez

Rare and Autoimmune Disease Unit, Internal Medicine Service, Virgen del Rocio University Hospital, Seville, Spain

***Corresponding author**: Dr. Jose Salvador García-Morillo, Rare and Autoimmune Disease Unit, Internal Medicine Service, Virgen del Rocio University Hospital, Seville, Spain, Tel: (+34) 678 421 588; E-mail: salvaymar@gmail.com

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Abstract

Combination of pulmonary fibrosis and emphysema (CFPE) is an entity defined in last years, with tobacco as the main etiological factor. Recent studies have associated it with connective tissue diseases and autoimmunity phenomena. The objective of this case series is to review some key aspects of CFPE from the diagnostic and therapeutic point of view, as well as its association with autoimmune diseases. This is a case series of three patients with CPFE associated with ANCA positive type MPO vasculitis.

We present three elderly male patients with important accumulated tobacco consumption who initially presented non-specific general and pulmonary symptom. They had elevated acute phase reactants and positive ANCA antibodies type MPO in blood. HRCT revealed areas of emphysema in the upper lobes and fibrosis in the lower ones . Initially, both patients presented normal result in spirometry but a marked decrease of DLCO. In the three cases biopsies were compatible with medium-vessel vasculitis. We apply corticosteroids associated with immunosuppressant therapy, obtaining different results in each cases.

Keywords: Emphisema; Fibrosis; Autoimmunity; Neutrophil anti-cytoplasm antibodies

Introduction

The combination of pulmonary fibrosis and emphysema (CFPE) is an entity defined by Cottin [1], identified more than 30 years ago in the Auerbach and radiological studies of Wiggins [2], which is characterized by areas of emphysema in the upper lobes, fibrosis in the lower and diffusion (DLCO) greatly diminished in functional studies. Spirometric patterns and volumes are usually normal [1], requiring high resolution computed tomography (HRCT) for diagnosis. Tobacco is the main etiological factor, present in the majority of those affected and has a high prevalence of associated pulmonary hypertension. There is no established treatment and the management is practically done by inference of what we know of pulmonary emphysema and idiopathic pulmonary fibrosis (IPF), which differs in prognosis and, based on recent studies, in presenting a greater association with connective tissue diseases and autoimmunity phenomena. The clinical cases of 3 patients suffering from CFPE and ANCA vasculitis type anti-myeloperoxidase (MPO) positive are presented. The review of the most novel aspects in the literature is included.

Presentation of the cases

Case 1: 60-year-old male, ex-smoker (accumulated history 80 packages/year) and with an history of spontaneous right pneumothorax 28 years ago treated with pleurodesis. Consultation for generalized myalgias (predominantly in the pelvic girdle), claudication of the temporo-mandibular joint, feverishness, weight loss of 5 kg and effort dyspnea that has been increasing in the last 2 months, having presented an isolated episode of diplopia of 20 minutes long. Dry bibasal crackles and bilateral apical hypoventilation are auscultated. Rest of the exploration (including ophthalmological evaluation and palpation of the temporal arteries) without pathological findings. Hemoglobin 10.9 g/l is detected with normal VCM and HCM, VSG of 110 mm/h and p-ANCA MPO positive. Rest of the autoimmunity study negative. Chest radiography shows signs of pulmonary hyperinflation in the upper fields and bilateral interstitial infiltrate with subpleural involvement. The HRCT reveals areas of centrolobular emphysema of subpleural predominance in upper fields and peripheral septal thickening with areas of honeycomb, microcysts and traction bronchiectasis in the lower lobes (Figure 1). In arterial gasometry PaO_2 66 mmHg, $PaCO_2$ 37 mmHg, pH 7.45, bicarbonate 25.3 mmol/l. The functional respiratory study does not show alterations (FEV1 86% -2610 ml, FVC 77.8% -2980 ml, FEV1/FVC 87.48%) with the exception of low DLCO (41%). It travels 480 meters without oxygenation drop in the gait test. The existence of pulmonary hypertension is ruled out by echocardiography. The histological pattern found in the lung biopsy is of usual interstitial pneumopathy with transformation in honeycomb and that of the temporal artery biopsy compatible with vasculitis with notable luminal obstruction. Systemic vasculitis of medium and large caliber arteries of the temporal is diagnosed with associated polymyalgia rheumatica and combination of pulmonary fibrosis and emphysema in early clinical stage. Treatment with prednisone 60 mg (which has been gradually reduced) and azathioprine 150 mg daily marked a significant clinical improvement. Currently without complete remission and continues in periodic monitoring in our consultations.

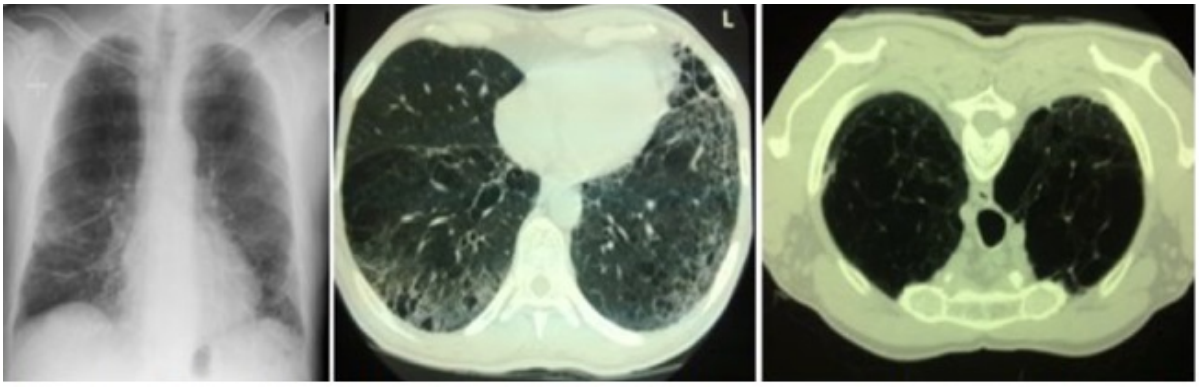

Figure 1: Chest X-ray. HCRT tórax base. HCRT tórax vertice.

Case 2: A 74-year-old male smoker (accumulated history 54 packages/year) without other medical history that consults due to fever, asthenia, malaise, generalized arthromyalgia and persistent non-productive cough without dyspnea or other associated symptoms. It presents elevation of inflammatory markers (PCR 211 mg/l, VSG 62 mm/h, ferritin 381 mg/dl, decrease in albumin and hemoglobin 8.9 g/dl with normal VCM and HCM) and deterioration of renal function (creatinine 1.38 mg/dl), being the rest of the normal blood test study. In urine it presents proteinuria (900 mg/24 hours), hematuria and leukocyturia. Neuroculture, blood cultures and sputum cultures (including smears and Lowenstein culture) negative. In ANCA MPO autoimmunity study positive to titers of 93 U/l, ANA, antiDNA and anti-basement membrane negative. The chest radiograph shows a bibasal interstitial infiltrate with microcystic areas and apical hyperinflation with air trapping data. The chest CT scan confirms the existence of a paraseptal emphysema in both upper lobes and areas of honeycomb, lung destruction, patched tarnished glass and traction bronchiectasis in the lower two thirds, highly suggestive of pulmonary fibrosis. Functional respiratory tests show a restrictive pattern without obstruction but with a 50% decrease in DLCO. It travels 352 meters in the 6-minute test. Renal biopsy shows active necrotizing lesions in glomeruli without intimal hyperplasia or arteriohyalinosis with the presence of crescents (5.88%) and endocapillary proliferation together with fibrinoid necrosis at the level of the vessel wall. ANCA MPO positive vessel vasculitis with renal and pulmonary involvement (CFPE) is diagnosed. Initially during admission he receives antibiotic coverage (ceftriaxone 2 g and levofloxacin 500 mg daily) and after diagnosis 3 intravenous boluses of 1 g of methylprednisolone are scheduled on consecutive days as well as a dose of 15 mg/kg adjusted for weight and renal function (650 mg) Receive 5 more monthly doses of cyclophosphamide, prednisone 60 mg/day in descending regimen and finally mycophenolate as maintenance therapy. The initial response is favorable, getting remission of activity, but lung function deteriorates and the patient dies in the following year.

Case 3: A 66-year-old male smoker (accumulated history 38 packages/year) with a history of rhinoconjunctivitis and asthma that consults for intermediate-duration fever and profuse verb sweating. At auscultation presents dry crackles, saturation at room air of 97%. It presents elevation of inflammatory markers (PCR 199 mg/l, ESR 89 mm/h), IgE elevated by 188 U/ml, the rest of the normal blood test. Blood cultures and negative serologies. Urine elemental without alterations. In an autoimmunity study, ANCA has positive MPOs at titres of 32.4 U/l, Rheumatoid Factor>300 U/ml and positive cryoglobulinemia. ANA, antiDNA and anti-basement membrane negative. A biopsy resulted in a vasculitis of a medium vessel. During the study, fibrotic tracts were observed mainly in the upper right lobe and bronchiectasis on the chest X-ray, confirming later in the chest CT scan the existence of emphysematous changes in the superior lobes and areas of fibrosis with panalization in the lower lobes. Spirometry shows a non-restrictive and unobstructed pattern. Initial diagnosis of PAN versus eosinophilic granulomatosis with polyangiitis so it was initially treated with prednisone 60 mg (with progressive decrease) and azathioprine 150 mg daily. Subsequently, mycophenolate mofetil 2 g per day as maintenance, achieving normalization of the acute phase reactants and the non-progression of pulmonary involvement in subsequent TACAR.

Discussion

The combination of pulmonary fibrosis and emphysema is an entity whose prevalence is estimated in 5%-10% of intestic pneumopathies [2]. Dyspnea (usually grade 3-4 of the MRC) is the most common symptom. For an early diagnosis and avoid underdiagnosis, we must keep it in mind in important active smoking patients (cumulative smoking history over 40 packages/year), over 65 years of age [3] in those who detect dry crackles in pulmonary bases and apical hypoventilation, with occasional acropachy [1]. Spirometry can be normal or suffer minimal variations, in contrast to a significantly reduced diffusion (DLCO) that allows the combined effects of pulmonary fibrosis and emphysema to be combined. In this way, DLCO becomes a fundamental parameter to determine the degree of disease as well as the chronic hypoxemia derived from it [4]. Although the radiological findings described in clinical cases are the most common, a normal chest X-ray would not exclude the diagnosis, so it requires visualization of basal fibrosis and apical emphysema on HRCT [5]. Even without considering the biopsy necessary for diagnosis, the most common pulmonary histological pattern, as in the 3 cases of the series, is the usual interstitial pneumopathy (NIU) [6]. An echocardiography is justified for screening of pulmonary hypertension (PH), since it is a prevalent complication (up to 47%-90%) and with prognostic involvement [2]. It is an independent mortality predictor [1] and 60% one-year survival is described if present. Valentin Fuster and his team propose cardiac MRI as an alternative due to the difficulty of interpreting echocardiographic results due to the presence of emphysema [7].

Smoking is assumed as the main etiological factor, as it is a constant in all cohorts studied [8], when it occurs in an individual with a genetic predisposition (the relationship with mutations of the SFTPC gene of the C protein of the pulmonary surfactant is known [9] as well as mutations of the TERT, TR and NAF1 genes of telomerases) [10]. In this way, the accumulation in the macrophage of the substances of the cigarette would serve as a trigger for the inflammatory process that would end in a parenchymal destruction and abnormal remodeling. Therefore, quitting tobacco would be the main preventive measure. Although there was initially speculation about the possibility of dealing with the coexistence of pulmonary emphysema and pulmonary fibrosis in the same patient, there are several studies that identify common pathogenic pathways and that aim to consider it a single entity. Highlight the increase in oxidative stress [11], the greater dysfunction of the parenchymal expression of caveolines, the overexpression of key molecules in the destruction and repair of the alveolar endothelium (TNFa, growth factor derived from platelets-PDGF and metaoloproteinases) [12] and the autoimmune alteration and loss of immune tolerance The relationship of this entity with autoimmune systemic diseases is a topical issue.

A series of 34 patients were already published describing their association with rheumatoid arthritis (53% of cases), limited systemic sclersosis (20% of cases) and other connective tissue diseases with lower percentages) [13].

Also recently a work has been published on the increased incidence of autoimmunity markers in patients with CFPE [14]. In the latter, 40 patients with CFPE were compared with 60 patients with IPF, with a greater presence of anti-nuclear antibodies (ANAs) (42.5% *vs.* 26.6%, $p<0.05$) and ANCAs (17.5% *vs.* 0%, $p<0.05$) in the case of CFPE. It is especially interesting that in the 7 cases of CFPE that presented positive ANCAs these were MPO type as in our series.

These data coincide with what was published by Tzelepis et al. [15], which describes a series of 7 cases in which there is a relationship between pulmonary fibrosis and microscopic polyangeitis (MAP), 3 of these patients diagnosed with biopsy and 4 others. with immunological alterations (positive ANCA MPO), clinical (mild or exertional dyspnea) or analytical (microscopic hematuria without proteinuria or renal function impairment) that could suggest the presence of a "hidden or subclinical" vasculitis. Results similar to those in our series where we have 1 patient with renal biopsy confirming MAP and two others with clinical and analytical data suggestive of vasculitis.

From the previously mentioned study it is also extracted that the presence of autoimmunity could give a better prognosis (mean survival 51 *vs.* 38 months, $p=0.052$), this being related to a greater presence of CD20 lymphocytes in the lung biopsy. In recent years, new evidence has confirmed these data [16] so that autoimmunity markers could be used as analytical and histological prognostic markers in the future.

Conclusion

We conclude that the CFPE is an entity described in recent years in which smoking plays a leading role and is characterized by a specific clinical, radiology and functional impairment. The clinical suspicion is important since in early stages it can go unnoticed since spirometry and simple radiology can be normal. A diffusion study and HRCT is necessary to arrive at the diagnosis. There is enough evidence to suspect in these cases the presence of autoimmune systemic diseases, having described a special association with ANCA vasculitis with MPO specificity, as is the case in the 3 cases we present. It remains to be defined if it really is a single entity, whether it is the association of 2 pathologies produced by tobacco or in some cases, the pulmonary expression of another systemic pathology.

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