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## *Cryptococcus neoformans* pleuritis in an immunocompetent patient☆

## *Pleuritis por* Cryptococcus neoformans *en paciente inmunocompetente*

*To the Editor:*

The genus *Cryptococcus* includes different species of encapsulated yeast fungi, of which only *C. neoformans* is considered a human pathogen. Its polysaccharide capsule confers virulence by protecting it from phagocytosis and complement activity. Four serotypes within this species have been described — A, B, C, and D — depending on the components of the capsule. Serotypes A and D are identified as C. neoformans var. *neoformans*, and antigens B and C as *C. neoformans* var. *gattii*. The 2 varieties differ both in their pathogenesis and their geographical distribution. *C. neoformans* var. *neoformans* is distributed worldwide and is associated with infections in immunocompromised patients, while *C. neoformans* var. *gattii* has been associated with infections in immunocompetent patients, and its distribution is more restricted to tropical and subtropical countries.[1]

*C. neoformans* var. *neoformans* can affect any individual, although it is more common in patients with a predisposing factor (HIV infection, use of immunosuppressive drugs, connective tissue disease, cirrhosis, etc.).[2]

Despite the fact that the pigeon feces are the most important source of infection, these animals do not suffer from the disease. Humans acquire *Cryptococcus* infection by the respiratory route, and transmission from person to person has not been proven. Although the infection tends to enter via the airways, pulmonary involvement is rare, while the most common presentation is neurological. Pulmonary lesions caused by *Cryptococcus* vary, and include nodules, masses, interstitial infiltrates, alveolar consolidation, and lymphadenopathy.[3,4] Pleural effusion, either isolated or associated with pulmonary disease is a rare manifestation.[2–6]

We describe a case of pleuritis caused by *C. neoformans* in an immunocompetent patient.

Our patient was a 78-year-old man with a history of chronic kidney disease stage 3a, permanent atrial fibrillation, congestive heart failure with preserved ejection fraction, alcoholic liver disease, and chronic obstructive pulmonary disease/sleep apnea hypopnea syndrome overlap (COPD + SAHS) receiving treatment with CPAP. He attended our clinic due to a 4 or 5-day-history of sudden onset right pleuritic pain, accompanied by increased dyspnea, cough with expectoration of mucus, and low-grade fever in the afternoon. His general status on physical examination was good, with blood pressure 139/68 mmHg, heart rate 83 bpm, axillary temperature 37.5 °C, $SatO_2$ 95 % baseline. Mobile right axillary lymphadenopathies were detected, with no palpable lymphadenopathies in other territories. Arrhythmias were heard on cardiac auscultation, and pulmonary auscultation revealed reduced breath sounds in the right lung base with bilateral rhonchi; no other significant findings were detected on physical examination.

Clinical laboratory tests were significant for mild anemia and raised inflammatory markers. Chest radiography revealed right pleural effusion.

A diagnostic thoracentesis was performed, and the drained fluid showed biochemical characteristics of exudate: pH 7.45, glucose 121 mg/dl, protein 4.1 g/dl, ADA 24.7 U/l, erythrocytes 25,200 µl, nucleated cells 3100 µl (polymorphonuclear 39 %, lymphocytes 23 %, macrophages 38 %, and reactive mesothelial cells). Pleural fluid, sputum, and blood were collected and sent for culture.

Diuretic treatment with furosemide was intensified and empiric antibiotic coverage started with ceftriaxone. On day 4 of admission,

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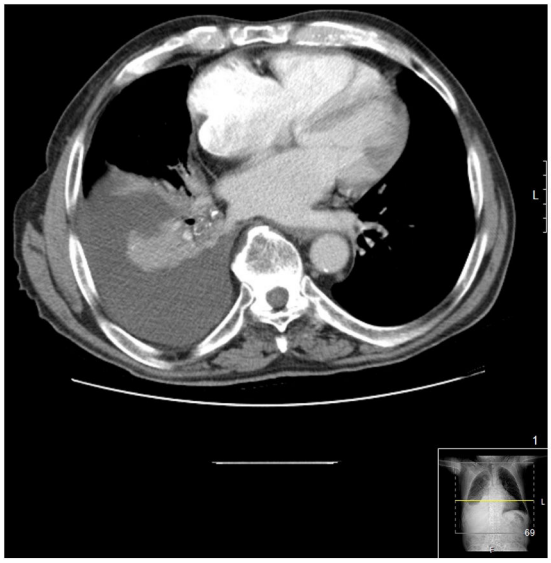

**Fig. 1.** Computed tomography showing right pleural effusion associated with loss of volume.

the patient was afebrile, with negative water balance and improved pleuritic pain and dyspnea. At this time, the microbiology laboratory reported isolation of yeasts in pleural fluid, so the thoracentesis was repeated, and blood cultures were collected again. A back of the eye study was normal, and HIV serology was negative. Treatment started with fluconazole.

Chest CT scan revealed right free-flowing pleural effusion 5 cm thick, causing passive atelectasis of the right lower lobe (Fig. 1), with no other changes.

Blood and sputum cultures were negative. The yeast was identified as *C. neoformans* by 2 different microbiological methods: the VITEK system® 2 (Biomerieux, Marcy l'Etoile, France) and MALDI-TOF mass spectrometry (Bruker). The yeast was also isolated in the second pleural fluid culture. Testing for cryptococcal antigen in serum was also requested, which was negative.

Treatment was switched to voriconazole 200 mg every 12 h and thoracentesis was performed for drainage, with subsequent resolution of the effusion. Treatment continued for a month on an outpatient basis. After completion of the antifungal treatment, the patient attended a subsequent check-up in the outpatient clinic, and had returned to baseline.

*C. neoformans* pleuritis is a rare entity, which occurs mainly in immunosuppressed patients. In a recent review[2] that included 25 cases of cryptococcal pleural effusion, 20 of the 25 patients had some type of immunosuppression; among the most common predisposing factors were HIV infection (7 cases), solid organ transplant (5 cases), or tumor disease (4 cases). In an earlier review[6] of 30 cases, underlying disease was documented in 17 cases, while 10 had no predisposing factor. In that cohort, most patients with cryptococcal pleural effusion had disseminated cryptococcosis, whereas localized chest infection was more common in immunocompetent patients.[6] Our patient, despite a previous diagnosis of alcoholic liver disease, presented no clinical, laboratory, or imaging data suggestive of advanced liver disease, which as we mentioned is one of the factors often associated with this infection.

Cryptococcal pleuritis can, therefore, occur in isolation, in association with lung consolidation or not, or in the context of disseminated cryptococcosis. For the diagnosis of cyptococcal pleural effusion, the organism must be isolated in a culture of pleural fluid or pleural biopsy.[4] In the event of disseminated cryptococcal disease, the detection of cryptococcal antigen in the blood could be useful. Our patient had isolated effusion due to *C. neoformans* with no pulmonary consolidation (ruled out on CT) or dissemination to other organs (which might explain why the cryptococcal antigen in serum was negative). Although *Cryptococcus* was isolated in our patient from 2 cultures of pleural fluid, cultures can be sometimes negative, given the small amount of inoculum present in the pleural fluid.[3,5] If the culture is negative, it may be helpful to test for cryptococcal antigen in pleural fluid (not carried out in our case), since the effusion is simply an inflammatory response to cryptococcal antigen.[5]

The mechanism of entry of the infection to the pleural space is usually by the pulmonary route, although the pleura could also be accessed by hematogenous spread. We believe the first route is the most likely in our case, and we speculate that his CPAP may possibly have been involved in the pathogenesis of this infection.[7] In this respect, we cultured the tubing and the humidifying fluid, which were negative, although these were sampled on Day 6 of admission, after the fluid had been changed, so we could not confirm this hypothesis.

In conclusion, cryptococcal pleuritis is a rare entity which can occur in immunocompetent subjects, and one that should be taken into account in the differential diagnosis of pleural effusion in this type of patients. Given the suspicion that the source of infection in our patient could have been the CPAP, users of these devices must be made acutely aware of the importance of their appropriate use and disinfection because of the serious consequences that can result from their incorrect use.

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## P.TYR1381X: Are We Facing a New Mutation of CFTR in a Patient With Severe Cystic Fibrosis?

### *P.TYR1381X: ¿Nos enfrentamos a una nueva mutación de CFTR en un paciente con fibrosis quística grave?*

*Dear Editor,*

Cystic fibrosis (CF) is the most frequent genetic disorder in the Caucasian race produced by the cystic fibrosis transmembrane conductance regulator (CFTR) gene disturbance. This gene, located on the long arm of chromosome 7, was first discovered by Andersen in 1938, although it was not until 1989 when it was identified as causing CF. This disease is transmitted in an autosomal recessive Mendelian inheritance pattern. Although it can be expressed phenotypically in different ways, it affects the exocrine epithelial cells of the respiratory system, the pancreas, the bile ducts, the sweat glands and the genitourinary system.[1]

In Spain, a decrease in the incidence of CF after the implantation of neonatal screening is recognized. However, the prevalence has increased[2,3] in relation to the greater survival of these patients due to the improvement in the quality of care and the new therapeutic strategies making a disease that was initially considered pediatric[4,5] become chronic.

The allelic heterogeneity of CFTR gene was described in the 1990s[6] and it has recently been shown that the complexity of the mutation spectrum is greater than previously known.[7]

Alonso et al. managed to identify in Spain a total of 121 mutations of the CFTR gene, which represents 96% of the 1,954 Spanish alleles studied. Twelve of them presented frequencies higher than 1%, the most frequent being p.Phe508del (also known as F508del). Those that have a frequency lower than 0.5% are considered rare mutations[7]. To date, there is a global registry of CFTR mutations in the CF Mutation Database (CFTR1)[8] and in the Clinical and Functional Translation of CFTR database (CFTR2) with constant updating,[9] although some very rare and of uncertain clinical significance mutations continue to emerge. The identification of these gene disturbances and the phenotypic characterization of these patients allow us to know better the functional importance of the CFTR gene. Because of this, homozygous patients are required for these specific mutations, in which all the phenotypic expression can be attributed to that specific genetic alteration although unfortunately they are not usually prevalent.

We present the case of a 19-year-old Caucasian male homozygous for the p.Tyr1381X mutation (legacy name: Y1381X; DNAc: c.4143C>A). It is a mutation of synthesis defect (type I) whose functional alteration resulting is the absence of protein synthesis and characterized by the substitution of the amino acid tyrosine at position 1381 of CFTR by a termination codon.

He was diagnosed with CF at 15 months old after admission for recurrent infections, diarrhoea and weight loss. The analysis of sweat test revealed that the concentration of chloride was 141 and 145 mEq/L. The first genetic analysis performed on him after diagnosis was negative but it was used a basic panel of mutations. A most advanced genetic study was carried out at 2015 and characterized the real mutation of which up to that moment only one case had been registered in CFTR1.[8] He was a full-term infant born before the CF neonatal screening implant. His birth weight was 2.9 kg, birth length 48 cm. Parental consanguinity was ruled out. His parents and his elder sister were carriers of this mutation but they were asymptomatic.

Until he was 15 years old the follow-up was performed by paediatrics. When he arrived at the Pulmonology Department he presented respiratory and digestive affectation, CF-associated arthritis and growth retardation. He presented chronic bronchial infection (CBI) by methicillin-sensitive *Staphylococcus aureus* (MSSA) since 14 years old without clinical repercussions. His treatment to date was: nebulized dornase alfa and hypertonic saline with hyaluronic acid (2.5 mg/24 h and 5 ml/12 h, respectively), budesonide/formoterol (160/4.5 μg/12 h), salbutamol (if need), azithromycin (250 mg three times per week) and respiratory physiotherapy. He presented CBI by *Pseudomonas aeruginosa* (PA) since 16 years old so treatment was started with nebulized colistimethate sodium (1 MIU/12 h) and the PA infection was eradicated after two years. This therapy was discontinued in that moment. The patient did not have PA infections again; however, the CBI by MSSA persisted in time until the present.

Nowadays he presents a rapidly progressive clinical deterioration, highlighting recurrent infections. Last year he had a moderate exacerbation that was managed ambulatory with oral antibiotics and two severe exacerbations that required hospital admission due to respiratory failure. Due to respiratory deterioration, nebulized treatment with vancomycin was started for MSSA. Thoracic CT showed generalized cystic bronchiectasis. The respiratory deterioration has led to the request for evaluation of lung transplantation being currently on the waiting list.

Other comorbidities are severe pancreatic insufficiency (pancreatic gland atrophy and diffuse fatty replacement), iron-deficiency anaemia and acute severe malnutrition in the context of recent exacerbations.

The lung function, weight, height and CBI evolution is summarized in Table 1.

Despite genetic counselling, progress in the detection methods of mutations causing CF and implantation of neonatal screening in recent decades, there is still a small percentage of very rare mutations which are being identified and whose phenotypic behaviour is unknown. Its recognition allows us to advance in the study of this disease, especially in those cases of homozygous since its