

permanente<sup>8,9</sup>. Sin embargo, en otras series llega a ser necesaria la administración de corticoterapia sistémica o incluso de inmunosupresores<sup>10</sup>. En aproximadamente un tercio de los pacientes con manifestaciones pulmonares suele darse un fracaso del tratamiento con glucocorticoides y precisan terapia supresora. Algunos ejemplos de inmunosupresión serían la azatioprina, con buenos resultados en el caso de Soma Kar<sup>7</sup>, aunque al contrario que el paciente que nosotros presentamos padecía una colitis ulcerosa; y por otro lado, el infliximab ha demostrado gran mejoría en la sintomatología de los pacientes con enfermedad inflamatoria intestinal, no solo por su papel en el control de las manifestaciones gastrointestinales, sino también en las pulmonares, como refiere Hayek<sup>10</sup>. La duración del tratamiento no está clara y varía mucho: desde 2 semanas en los más cortos hasta 3 meses en los más largos. En nuestro caso el tratamiento se mantuvo a dosis plenas durante un mes y, posteriormente, se redujo durante los 2 meses siguientes hasta su suspensión.

El hecho de que la enfermedad intestinal inflamatoria pueda dar lugar a manifestaciones pulmonares todavía es desconocido. Se sabe que el proceso embrionario de formación del tracto gastrointestinal y del aparato respiratorio procede de la misma parte de la estructura embrionaria y tienen una estructura epitelial similar, por lo que esto podría explicar la afectación pulmonar en esta entidad. Sin embargo, se han planteado otras múltiples alternativas como la disbiosis bacteriana, la contaminación medioambiental o incluso factores genéticos<sup>1</sup>. Por esto, en todo paciente con enfermedad inflamatoria intestinal debe tenerse en cuenta, dentro del diagnóstico diferencial, la existencia de manifestaciones propias de su enfermedad de base, especialmente en aquellos pacientes que presenten tos y fiebre sin un claro patógeno infeccioso. Pese a que todavía se cree que la incidencia de estas manifestaciones es baja, es probable que exista un infradiagnóstico, pues muchos pacientes se clasifican como asmáticos ante su buena respuesta a corticoterapia inhalada y dada la similitud en las pruebas diagnósticas<sup>6,7</sup>. Por ello, debemos tener en cuenta esta posibilidad diagnóstica cuando nos encontremos frente a estos pacientes.

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## Diagnostic Performance of a Lateral Flow Assay for the Detection of Alpha-1-Antitrypsin Deficiency



### Rendimiento diagnóstico de un ensayo de flujo lateral para la detección de la deficiencia de alfa-1 antitripsina

Dear Editor:

Despite of the demonstrated benefits of an early diagnosis and treatment on disease progression,<sup>1</sup> today the diagnosis of alpha1-antitrypsin deficiency (AATD) remains a challenge in daily clinical practice. Different barriers have been identified during the past years including a low suspicion level mainly based on a misconception of the disease among clinicians, who only suspect the disease in a selected and infrequent group of patients.<sup>2</sup> As a consequence, the degree of alpha1-antitrypsin (AAT) serum determination is frequently insufficient.<sup>3,4</sup> Accordingly, different initiatives have been developed to improve diagnosis over the past years. Based on lateral-flow paper-based technologies,<sup>5</sup> the Alphakit Quickscreen (Grifols, Barcelona, Spain) has been marketed in Europe for the identification of the Z protein (PiZ) in serum. Therefore, the test allows the identification of the Z allele homozygous, heterozygous and carries

The opportunities for the diagnosis of AATD of such a test are clear, since the on-site rapid and accurate identification of PiZ carriers may help identify AATD cases at an early stage with implications for management and family screening. However, the diagnostic accuracy of this test has been scarcely studied. In the one real world evaluation of its performance available,<sup>6</sup> the evaluation of the test's ability to detect the PiZ protein showed a specificity of 97.8%, sensitivity of 73.8%, negative predictive value of 98.9%, and positive predictive value of 58.5%. Of note, after exploring the test-performance with different prevalence pre-test probability, the authors found lower negative predictive values in a population with a very high pre-test probability. Therefore, the authors concluded that the device could be used as an appropriate tool to exclude AATD in primary care and in the overall COPD population, except in patients with a high a priori-probability of AATD. Additionally, an added finding was that all false negatives ( $n = 11$ ) were heterozygote Pi\*MZ samples, with a correct identification of ZZ and SZ genotypes. In this context, an unexplored population of special interest is that with a low a priori pre-test probability of severe AATD defined as those with AAT serum concentration > 50 mg/dl which are associated with increased risk for COPD<sup>7</sup>. The identification of the Z allele in this population may help identifying Z carriers and advance in the early identification of treatable cases.

**Table 1**  
Results of the Alphakit Quickscreen test and the genotyping.

Genotype	Complete cohort (n = 16)		Alphakit Quickscreen negative (n = 7)		Alphakit Quickscreen positive (n = 9)	
	N	AAT <sup>a</sup>	N	AAT <sup>a</sup>	N	AAT <sup>a</sup>
MM	2	116.1 ± 7.6	1	110.7	1	120.0
MZ	4	83.4 ± 12.5	0	–	4	83.4 ± 12.5
SM	4	104.5 ± 9.8	4	104.5 ± 9.8	0	–
SS	1	87.0	1	87.0	0	–
SZ	5	79.3 ± 25.9	1	56.5	4	85.0 ± 26.0

<sup>a</sup> Alpha1 antitrypsin serum concentration expressed as mg/dL.

Data are expressed as absolute frequencies and mean ± standard deviation according to the variables' nature.

We performed a prospective, single-center, observational, cross-sectional, real-world analysis on the performance of Alphakit Quickscreen. Following the Spanish recommendations,<sup>8</sup> all patients referred to our COPD-dedicated outpatient clinic from January 2016 to July 2018 for a diagnosis of COPD had a serum AAT determination by nephelometry and those between 50 and 120 mg/dL, had an Alphakit Quickscreen determination done. The test was performed complying with all the requirements of the manufacturer in the conservation and performance of the test. The study was completed by allele-specific genotyping. The diagnostic profile including the sensitivity, specificity, and the positive and negative predicted values for the identification of the Z allele was calculated together with the 95% confidence interval (95%CI). Data are expressed as absolute (relative) frequencies and mean (standard deviation) according to the variables' nature.

The sample was composed of 16 subjects: 11 (68.8%) males, 58.4 (15.3) years of age, 6 (37.5%) current smokers, tobacco history 52.7 (31.7) pack-year, body mass index 27.7 (6.8) kg/m<sup>2</sup>, of which 12 (75.0%) fulfilled COPD diagnostic criteria with a post-bronchodilator FEV<sub>1</sub> of 64.3 (18.0) %. Serum AAT concentrations varied from 56.5 to 120.0 mg/dL, with a mean value of 91.7 (20.7) mg/dL. The distribution of the Z alleles according to the Alphakit Quickscreen result is presented in Table 1. The prevalence of the Z allele in this highly selected low-risk population of cases was 56.2% (95%CI 31.9–80.5). The diagnostic profile of the test resulted in a specificity of 85.71 (95%CI 68.5–100), sensitivity 88.9 (95%CI 73.5–100), negative predictive value 85.7 (95%CI 68.5–100), and positive predictive value 88.9 (95%CI 73.5–100). We detected one false negative (a SZ case with AAT serum concentration of 56.5 mg/dL) and one false positive (a MM case with AAT serum concentration of 120 mg/dL).

The Alphakit Quickscreen represents an attractive diagnostic method since it explores the presence of the Z protein using a non-invasive method and is freely distributed in the country by Grifols (Grifols, Barcelona, Spain). Our data show the diagnostic profile of Alphakit Quickscreen device in an a priori low probability of AATD cohort and additionally describing one case of a false negative in a SZ patient and a false positive in a MM case. The main strength of our approach is the exploration of a specific subgroup of patients in which the test may be useful. The limitation is the small sample size which is intrinsically associated with the population selection in a rare disease like AATD. Therefore, these findings should be confirmed in an independent cohort that includes these types of patients.

The evaluation of the diagnostic profile of new diagnostic techniques is a necessary step before wide clinical implementation. The one previous real-world available study evaluated 1019 samples in test-naïve COPD patients from 9 centers in Spain and 10 centers in Germany. Patients included were ≥30 years of age and with a confirmed diagnosis of COPD, with no exclusion criteria regarding the AAT serum levels. Our study continues the evaluation of the Alphakit Quickscreen in a specific population which may be of interest for the identification of Z-allele carriers. Our area has a lower

prevalence of PI\*Z as compared to the rest of the country.<sup>9</sup> As a quick, easy, point-of-care test, this may have implications in the use of this test in future diagnostic algorithms. Although this device allows for rapid analysis at the patient's point of care, its actual position within a diagnostic algorithm as a screening tool needs to be assessed.

Another interesting finding is the identification of one case of SZ which was a false negative, as compared to the previous analysis in which all false negatives were MZ.<sup>6</sup> False negatives in a lateral-flow analysis may be related to preservation, technical performance or correct interpretation, rather than the specific genotype. Therefore, it is expected that false negatives may affect different Z-allele carriers irrespective of the final genotype, as the study of the test expands. Moreover, it would be interesting to confirm the genotype in all false negative and false positive cases by complete sequencing of coding exons of AAT gene.

In summary, the evaluation of the performance of Alphakit Quickscreen in an a priori low risk of AATD population shows a diagnostic profile that allows it to be considered as a potential step in the diagnostic algorithm of AATD diagnosis. Additionally, this device represents a great opportunity to increase the awareness of AATD.

**Conflicts of interest**

JLLC has received during the last 3 years personal fees or non-financial support from Grifols and CSL Behring. The rest of the authors declare no conflicts of interest.

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## Cystic Metastasis of a Giant Cell Tumor Causing Recurrent Spontaneous Pneumothorax

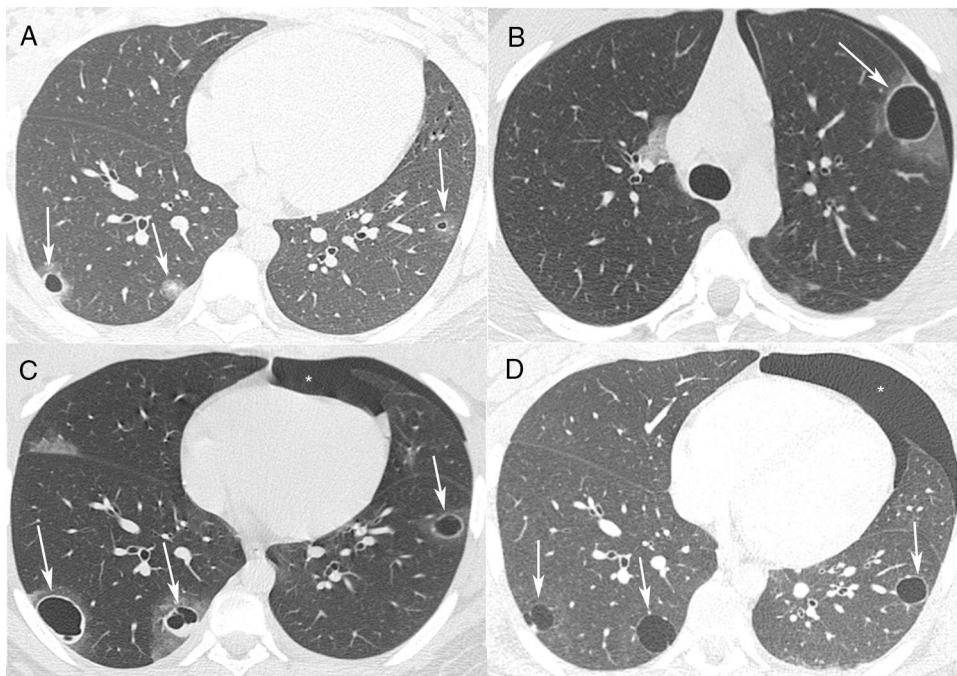


### Metástasis quística de un tumor de células gigantes causante de neumotórax espontáneo recurrente

Dear Editor:

A 17-year-old male was admitted to the Emergency Department with cough and episodes of hemoptysis. The patient had a history of a giant cell tumor (GCT) in the left tibia, resected 6 months previously. Chest computed tomography (CT) revealed pulmonary nodules, some of which were cavitated (Fig. 1A). Laboratory test findings were unremarkable. The patient's sputum was negative for acid-fast bacilli. He was referred for fiberoptic bronchoscopy with bronchoalveolar lavage. The bronchoalveolar lavage fluid contained a small amount of blood, and was negative for neoplastic cells.

Cultures were negative for fungus and bacteria. Video-assisted thoracoscopy was performed, and the biopsy findings from one of the nodules were compatible with GCT metastasis. The patient started a new chemotherapy cycle. Four months later, he had an episode of chest pain associated with hemoptysis. A new CT examination showed a left pneumothorax, and cavitated thick-walled nodules with ground-glass halos (Fig. 1B and C). The pneumothorax was drained. The patient evolved well, with pulmonary re-expansion. Eight months later, he had a new episode of chest pain and dyspnea. CT showed a spontaneous left pneumothorax, and evolution of the cavitated nodules into thin-walled cysts (Fig. 1D). In this phase, the patient presented metastasis to intraabdominal lymph nodes in addition to the pulmonary metastases. He underwent new chest drainage and pleuroscopy with bilateral pleurodesis through the intrapleural instillation of talc. During pleuroscopy, pleural metastases were detected. The patient underwent a chemotherapy regimen with six cycles of doxorubicin and cisplatin, which



**Fig. 1.** (A) Axial chest CT with pulmonary window settings shows bilateral small pulmonary nodules, two of which are cavitated (arrows). (B, C) CT performed 4 months later demonstrates a left spontaneous pneumothorax (asterisk) and growth of the nodules, which now present with relatively thick walls and ground-glass halos (arrows). (D) CT performed 1 year after A shows a new left pneumothorax (asterisk) and evolution of the cavitated nodules into thin-walled cystic lesions (arrows).