Table 1
Characteristics of the Subgroup of Patients With Life-threatening Exacerbations.

Patient	Age (years)	Sex	Smoking	Allergies	pH on Admission	$PaCO_2$ on Admission	Eosinophils (cells × $10^3/\mu l$)	OTI/MV	NIMV
1	22	M	No	Yes	7.55	22	1770	No	No
2	35	M	No	Yes	7.23	56	0	Yes	No
3	40	M	No	Yes	7.13	54	0	Yes	No
4	22	M	No	NS	7.31	42	720	No	No
5	43	F	Yes	Yes	7.30	43	340	No	Yes
6	30	M	Yes	No	7.26	59	0	Yes	No
7	34	F	No	NS	7.35	36	1230	No	No
8	20	F	No	NS	7.34	43	140	No	No
9	29	F	Yes	Yes	7.43	38	290	No	No
10	17	F	No	Yes	7.22	45	330	Yes	No

MV: mechanical ventilation; NIMV: non-invasive mechanical ventilation; NS: non-significant; OTI: orotracheal intubation.

with inhaled treatment in this type of patients is taken into account, as it would help maintain high effectiveness in the prevention of serious exacerbations. We are, however, aware of the difficulty in identifying these patients, and community pharmacists are probably in a better position to detect them when they come for rescue medication, and these professionals would therefore be another key link in the chain of prevention and control of asthma.

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Solitary Pulmonary Nodule as a Form of Presentation of Cryptococcosis in a Renal Transplant Recipient☆

Nódulo pulmonar solitario como forma de presentación de la criptococosis en el trasplantado renal

To the Editor,

The presence of a solitary pulmonary nodule (SPN) in transplanted patients always raises the possibility of a malignant lesion, but the causes of SPN are very diverse, and infection is another common etiology.[1] *Cryptococcus neoformans* lung infection has a low incidence and rarely presents with isolated lung involvement.[2]

We report the case of a 46-year-old man with terminal chronic kidney disease caused by reflux nephropathy, renal transplant from a cadaver donor 10 years previously, receiving immunosuppressive treatment with prednisone, tacrolimus, and sodium mycophenolate. He attended a routine follow-up visit, where he was seen to be totally asymptomatic, with no suspicious respiratory or infectious clinical symptoms. No significant findings were made on physical examination. Chest X-ray revealed an ovoid lesion in the posterior segment of the right upper lobe (RUL), 12 mm in diameter, not observed in the study performed 1 year previously. The lesion was explored in greater depth with a chest CT, which showed a lung nodule suggestive of neoplasm in the RUL (Fig. 1), consistent with stage IA (T1aN0MX). The PET scan showed pathological uptake of this lesion, so malignancy was suspected. The nodule was resected surgically via an atypical segmentectomy with diagnostic and therapeutic intent.

The histological study reported necrotizing granulomatous inflammation with the presence of small rounded structures, heterogeneous in size and with frequent fragmentation, located

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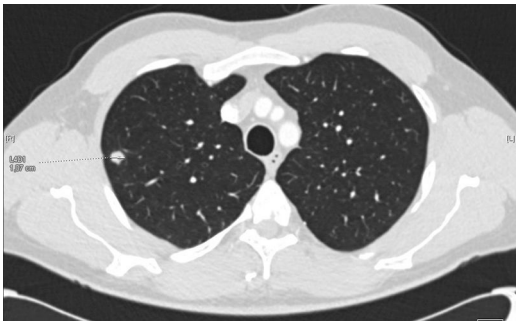

Fig. 1. Chest CT showing a solitary nodule 1 cm in diameter in the right upper lobe.

predominantly within the cytoplasm with signs indicating budding, grayish or eosinophilic on hematoxylin–eosin staining. Stains performed for fungal structures were positive for periodic acid-Schiff (PAS), Grocott's methenamine-silver, mucicarmin, and Alcian Blue, and negative for Ziehl–Neelsen staining, so morphologically the microorganisms were indicative of cryptococcus.

Microbiological testing was completed with serologies that were negative for both *C. neoformans* and human immunodeficiency virus antibodies. Brain CT scan showed no pathological findings, so lumbar puncture was not performed and additional antifungal treatment was not started. The patient subsequently made good clinical progress and currently remains totally asymptomatic.

Fungal infections are the third cause of infection in solid organ transplantation.[3] Specifically, the prevalence of *C. neoformans* infection in kidney transplantation is low, affecting 0.5%–2.8% of transplanted patients, but it is the third leading cause of fungal infection after *Candida* spp. and *Aspergillus* spp.[3]

C. neoformans is an encapsulated yeast present in soil contaminated with bird and bat droppings.[4] Infection is acquired by inhalation of the microorganism,[2,4] and the main form of host defense is innate and T-cell-mediated immunity,[5] probably explaining the predisposition to this disease among individuals receiving immunosuppressive treatment.[6] The most frequent form of infection is reactivation of latent microorganisms acquired in a previous infection.

The annual incidence of cryptococcosis has been calculated at more than 2:1000 renal transplant patients. Some authors believe that the incidence is increasing because of the increased survival of these patients,[7] while others, in contrast, report that the incidence remains unchanged.[8] The mean time between transplantation and the onset of cryptococcosis is 25 to 33 months, so presentation in our case is unusually late (120 months). Mortality is as high as 20%[7] and appears to be greater if the infection appears in the first year after transplantation,[8] when mortality is between 20% and 27%.[9]

Clinical manifestations of cryptococcal infection in the transplanted population are often non-specific and depend on the organ involved. Central nervous system (CNS) involvement, such as subacute meningoencephalitis, is the most common form of clinical presentation.[10] The second most affected organ is the lung.[2] The clinical manifestations of this form cover a broad spectrum, from acute processes such as pneumonia or pleuritis to radiological findings in asymptomatic patients, especially single nodule or multiple nodules observed on a routine chest X-ray.[11] The importance of this form of presentation lies in the fact that the lung is the gateway to disseminated infection, so an intensive diagnostic and therapeutic approach should be taken even in asymptomatic infection. After clinical reassessment, in the absence of neurologic symptoms, negative brain imaging, lack of uptake in PET testing at other levels, and negative serologies against cryptococcus, disseminated disease and CNS involvement could be excluded in our patient.

Microbiological diagnosis of pulmonary cryptococcosis can be confirmed by culturing the fungus in a sputum sample or by detecting cryptococcal antigen in serum.[12] Serological detection usually means that the infection is disseminated, which always requires the disease to be ruled out at other levels, especially CNS.[13]

Another way to diagnose this infection, as in the case presented, is by histological study of a biopsy or surgical specimen, demonstrating the presence of encapsulated yeasts with the usual fungal stains such as PAS and Grocott, and especially mucin, mucicarmin and Alcian blue stains, since the *Cryptococcus* genus is the only frequently pathogenic fungus that produces mucinous capsular material.[14]

Fluconazole may be used in mild forms of cryptococcal lung infection. In severe cases with diffuse pulmonary infiltrates or in the context of disseminated infection, treatment is based on amphotericin B combined with flucytosine.[15] Surgical treatment, as described, may be indicated in case of diagnostic uncertainty or therapeutic failure. Finally, because infection after transplantation is exceptional and occurs late, antifungal prophylaxis is not indicated.

In conclusion, cryptococcal infection should be considered in the differential diagnosis of SPN in immunocompromised patients, such as the transplanted population, and the diagnostic and therapeutic approach should be proactive as the respiratory tract is considered the gateway to disseminated infection.

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Descriptive Study of the Effect of Methodology in the Measurement of Sniff Nasal Inspiratory Pressure (SNIP) in a Healthy Population☆

Estudio descriptivo sobre la influencia de la metodología en la medición de la fuerza inspiratoria máxima en nariz (SNIP) en población sana

To the Editor,

Inspiratory muscle dysfunction is associated with many diseases,[1–4] and leads to a loss of quality of life and a worse prognosis for patients.[5–8] In clinical practice, several tests are used to quantify inspiratory muscle function.[1] Current recommendations advise measuring muscle strength during maximum inspiration at the mouth (maximum inspiratory pressure [MIP]) and the nose (sniff nasal inspiratory pressure [SNIP]).[1,2,9] The methodology for determining MIP is well defined,[1] but methodological variations appear in the maneuver for determining SNIP. One of the variations is the lung volume from which point the maximum inspiratory force maneuver is initiated. Some authors perform it from functional residual capacity (FRC),[1,2,9,10] while others do it from residual volume (RV).[11,12] There are also methodological differences with respect to leaving the contralateral nostril open or occluding it.[9–11]

The aim of this study, then, was to analyze the effect of 3 different methodological factors (occlusion/opening of the opposite nostril, lung volume from which the maneuver is performed, and graphical incentive) on SNIP values.

This was a cross-sectional, blinded study in healthy volunteers (health workers). The study was conducted with the approval of the ethics committee of the hospital, and all subjects signed informed consent. Individuals with symptoms of nasal obstruction or history of smoking, any chronic drug use, and alterations in forced spirometry were excluded. SNIP was measured with the subject seated and using a modified device inserted into the nostril and connected to a pressure gauge (TSD 104, Biopac Systems, Goleta, CA, USA), the signal of which was recorded by a digital polygraph (Biopac Systems).[12] Ten SNIP measurements were made with each of the methodological variants, and the best value was selected.[10] First, the influence of opening or occlusion of the nostril contralateral to the one being measured was studied. The influence of the expiratory lung volume from which the maneuver was performed was then studied, first from RV and then from FRC. Finally, the influence of the graphical incentive was studied, first without and then with visual stimulus (graphics on the computer screen). Each subject performed the same complete assessment twice at intervals of 24 h between each procedure. Results are presented as mean value±standard deviation. Variables were compared using the Student's *t* test. Data were analyzed using SPSS version 25.0 (IBM, Armonk, NY, USA), setting statistical significance at a *P* value ≤.05. A total of 35 volunteers (24 women/11 men), aged 28±11 years, were included, giving 70 assessments overall. The effect on SNIP values of the 3 methodological factors analyzed is shown in Table 1. SNIP performed with occlusion of the contralateral nostril produced better values than those performed with the opposite nostril open (*P*=.01). There were no statistically significant differences between SNIPs performed from FRC or RV (*P*=.1). SNIP performed with visual stimulus showed better values than SNIP performed without visual stimulus (*P*=.04).

This study shows that, in healthy subjects, some of the variations in the SNIP maneuver technique influence the values obtained and therefore would not provide a true picture of the strength of the inspiratory muscles. SNIP normal values have been defined by performing inspiration from FRC, without occlusion of the contralateral nostril or graphical incentive.[9]

Some authors, mainly when assessing patients with neuromuscular diseases, perform SNIP measurements by beginning the maneuver from RV.[11,12] We did not find that this alternative SNIP maneuver influenced SNIP values. However, the ease of performing the forced inspiratory maneuver when starting from FRC or from RV should also be evaluated. Although this was not assessed in our study, logically the maneuver would be easier to perform from FRC.

Another of the methodological modifications is occlusion of the nostril contralateral to the one in which SNIP is measured.[10,11] Studies in patients with neuromuscular diseases have reported that the determination of SNIP with the opposite nostril occluded produces higher values.[12,13] Indeed, an improvement in SNIP values when performed with the occlusion of the other nostril was also detected in our study. This improvement in SNIP values in patients with neuromuscular diseases following occlusion of the opposite nostril might fail to correctly show the strength of the inspiratory muscles,[12,13] which is a prognostic factor for these patients.[3]

Finally, in some pulmonary function tests, mainly spirometry, graphical incentives have been used for several years to facilitate the performance of the maneuver.[14] The use of graphical incentives impacts on SNIP by helping the subject achieve higher values. Therefore, use of this methodological modification during the measurement of SNIP should be reported.

Table 1
Description of the Variation in SNIP Values Based on the 3 Factors in Healthy Subjects.

SNIP, cmH_2O	Expiration to residual volume	Expiration to functional residual capacity	*P*
	95±25	91±23	n.s.
	Open nostril	Closed nostril	*P*
	83±15	90±19	**
	No graphical incentive	Graphical incentive	*P*
	83±22	91±24	*

n.s.: not significant; SNIP: nasal pressure during maximum inhalation.
* *P*<.05.
** *P*<.01.

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