1 - 2023

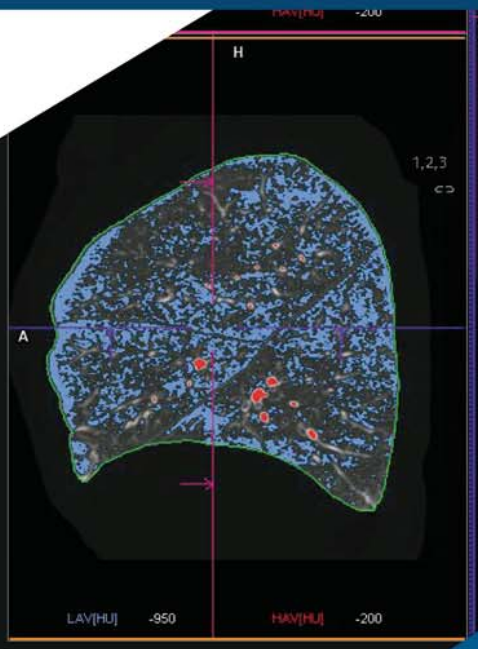
ISSN 2594-1526

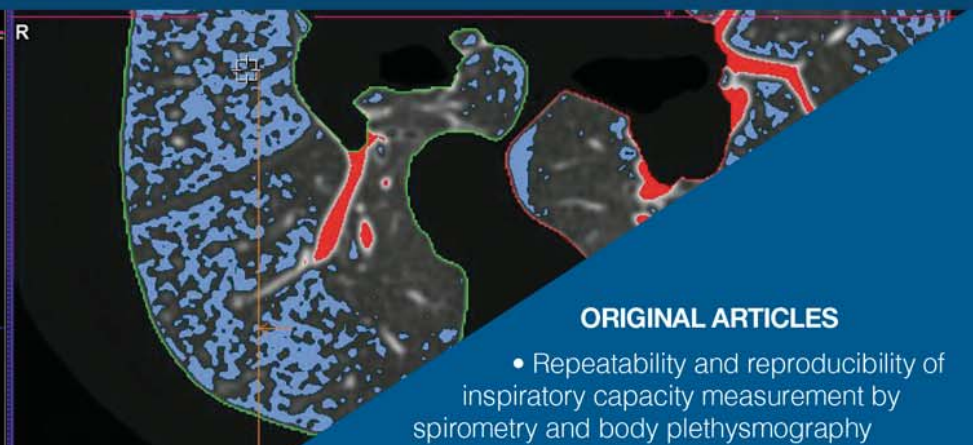
VOL. 82 NO. 1 JANUARY-MARCH, 2023

NCT

Neumología y Cirugía de Tórax

Functional lung imaging in chronic obstructive pulmonary disease phenotypes: a complementary vision





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Volume 82 / Number 1 / January-March 2023

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Neumología y Cirugía de Tórax
Vol. 82 - No. 1 / January-March 2023

Editorial
doi: 10.35366/114222

Functional lung imaging in chronic obstructive pulmonary disease phenotypes: a complementary vision

Imagen pulmonar funcional en los fenotipos de la enfermedad pulmonar obstructiva crónica: una visión complementaria

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In relation with the review article entitled «Lung Stereology in chronic obstructive pulmonary disease: pulmonary functional exploration imaging examination» which exposes and comments on the virtues of some of the advanced imaging techniques and their association with clinical and functional variables at an appropriate time, given the new and the old classifications of chronic obstructive pulmonary disease (COPD), rekindled and proposed in the last version of the GOLD Report 2023.[1]

Within the current definition of COPD as a condition characterized by bronchitis/bronchiolitis and emphysema as the main causes of persistent, irreversible and progressive obstruction of the airway and, therefore, being the traditional diagnostic instrument the post-bronchodilator spirometry according to the ratio of the forced expiratory volume in one second on force vital capacity (FEV_1/FVC <0.70),[1] it has been observed that this criterion shows limitations as it does not have a high sensitivity in the younger population under 50 years of age with an important subdiagnosis.[2]

Other functional respiratory tests have been analyzed in terms of their performance, such as the Carbon Monoxide Diffusing Capacity (DLCO), which when compared with the spirometry in smokers predicted better the occurrence of COPD in medium term.[3]

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How to cite: Hernández-Zenteno RJ, Pérez-Padilla JR. Functional lung imaging in chronic obstructive pulmonary disease phenotypes: a complementary vision. Neumol Cir Torax. 2023; 82 (1): 5-6. https://dx.doi.org/10.35366/114222

With the new advanced imaging techniques that have given rise to spatial stereology (image by sections) and the great technological development of imaging of functional type (pulmonary ventilation and perfusion) in which structural changes have been described in subjects with normal spirometries and with COPD[4] and who, in addition, show affectation in the other pulmonary function tests[4] and present the same level of symptoms as individuals with COPD,[5] we believe that this approach by imaging will provide data and validate, in a certain way, these classifications that have originated controversy, as to whether they represent the preamble of COPD and whether they should receive some type of intervention.[1]

Early COPD[1] in biological terms refers to the onset of the mechanisms (inflammatory at the biochemical and cellular level)[6] that lead to the typical lesions of the disease and that, it is accepted, may be present many years before irreversible obstruction is declared.[7] This approach differs and is far from the early clinical onset of symptoms, the functional limitation and the evident structural abnormalities that may be set in long after the initial preclinical changes seen in «healthy» smokers (normal smokers).[8]

Functional pulmonary imaging (FPI) or stereology will clarify how these structural damages develop and associate them with inflammatory parameters, such as the dilemma of smokers with normal spirometry who show several forms of phenotypes[8] discussed in the GOLD Report 2023[1] and that deserve to be discussed from this point of view.

Mild COPD should not be interpreted as an early stage of the disease in young people, but merely as a degree of severity that can occur at any age and progress or not over time.[9] In this case, the potential stereological findings would

have more congruence because there is already a level of obstruction, even if it is mild.

Young COPD may include patients who never reached normal maximum pulmonary function in their youth or who begin premature functional decline from infections in childhood; it does not necessarily have to be a mild disease, rather it may have a major impact on the health.[10] In this phenotype one would expect to find morphological changes of the airways and entrapment by densitometry, as well as incipient functional changes of diffusion and perfusion that needed to be defined.

Pre COPD is where there are symptom and structural or functional abnormalities detectable in presence of normal spirometry, which may or may not develop chronic obstruction (COPD) over time.[11] The term pre-COPD does not necessarily mean to evolve into the disease; (IPF), the diffusion and perfusion alterations, the changes of the airway and densitometry must be present to define and predict those who will become patients.

Finally, PRISm (preserved ratio impaired spirometry) describe a $FEV_1/FVC \geq 0.7$ but a $FEV_1 < 80\%$ post-bronchodilator; in a good proportion of patients, if not in the majority, it is associated with the development of COPD over time; and the more structural lesions observed on chest computed tomography (CT), the greater the risk of COPD installation.[12] In this situation, the challenge is to demonstrate the possible benefit of a treatment on the functional changes by IPF; perhaps this condition is the one that involves more structural alterations that influence the conversion to COPD.

For all these reflections, stereology or IPF opens a complementary portal to traditional pulmonary function tests by knowing the volumetry, air entrapment through densitometric analysis, the morphology of the airways (thickening of the wall and the area of the bronchial lumen), as well as other functional techniques to assess ventilation, diffusion and perfusion through dual energy CT, multi detector perfusion CT, perfusion magnetic resonance (with xenon, helium and krypton), positron emission tomography (PET) and single photon emission CT (SPECT), definitely, they will give more information for the study and approach of phenotypes and classifications where there are gaps in natural history and where spirometry does not finish defining what we should do.

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NCT
Neumología y Cirugía de Tórax
Vol. 82 - No. 1 / January-March 2023

Original

doi: 10.35366/114223

Repeatability and reproducibility of inspiratory capacity measurement by spirometry and body plethysmography

Repetibilidad y reproducibilidad de la capacidad inspiratoria medida por espirometría y por pletismografía corporal

Claudia Vargas-Domínguez,* Juan Carlos Vázquez-García*

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ABSTRACT. Introduction: the variability between measurements of inspiratory capacity (IC) by spirometry or plethysmography have not been completely described. The objective of this study was to describe the repeatability between the different IC maneuvers measured by slow spirometry and its reproducibility compared with body plethysmography. **Material and methods:** this is a descriptive, cross-sectional and prospective study of a sample of healthy adults who completed IC measurements by slow spirometry by two different maneuvers and by body plethysmography. **Results:** a total of 49 participants (27 men and 22 women) with a mean age of 33.2 ± 8.3 years (26 to 65 years) were included. The repeatability of the IC was ≤ 150 mL in 96% of the subjects for spirometry maneuvers while for plethysmography it was 78% of the participants. The correlation (Pearson's r) was 0.95 between slow spirometry maneuvers and 0.87 and 0.88 compared with plethysmography. The agreement between measurements showed potential errors of up to 576 mL between spirometry and up to 936 mL with plethysmography. **Conclusions:** the IC measurement by slow spirometry reached a repeatability of 150 mL or less in 96% of the participants, while by plethysmography it was only in 78% with potential errors close to one liter compared to plethysmography. This study supports the current recommendation of repeatability of 150 mL for the IC measurement by spirometry.

Keywords: inspiratory capacity, spirometry, repeatability.

RESUMEN. Introducción: la variabilidad entre mediciones de capacidad inspiratoria (IC) por pletismografía o espirometría no han sido completamente descritas. El objetivo de este estudio fue describir la repetibilidad entre las diferentes maniobras de IC medida por espirometría lenta y su reproducibilidad comparada con pletismografía corporal. **Material y métodos:** se trata un estudio descriptivo, transversal y prospectivo de una muestra de adultos sanos, quienes completaron mediciones de IC por espirometría lenta por dos maniobras diferentes y por medio de pletismografía corporal. **Resultados:** se incluyeron un total de 49 participantes (27 hombres y 22 mujeres) con una edad promedio de 33.2 ± 8.3 años (26 a 65 años). La repetibilidad de la IC fue ≤ 150 mL en 96% de los sujetos para las maniobras de espirometría, mientras que para la pletismografía fue de 78% de los participantes. La correlación (r de Pearson) fue de 0.95 entre las maniobras de espirometría lenta y de 0.87 y 0.88 comparado con pletismografía. La concordancia entre mediciones mostró errores potenciales de hasta de 576 mL entre espirometría y de hasta 936 mL con pletismografía. **Conclusiones:** la medición de IC medida por espirometría lenta alcanzó una repetibilidad de 150 mL o menos en 96% de los participantes, mientras que por pletismografía fue sólo en 78% y con errores potenciales cercanos a un litro comparado con pletismografía. Este estudio soporta la recomendación vigente de repetibilidad de 150 mL para la medición de IC espirométrica.

Palabras clave: capacidad inspiratoria, espirometría, repetibilidad.

Abbreviation:

Vd = volume difference
EELV = end expiratory lung volume
COPD = chronic obstructive pulmonary disease
FEV_1 = forced expiratory volume in one second
FRC = functional residual capacity
FRC_{pleth} = plethysmograph RFC
FVC = forced vital capacity
IC = inspiratory capacity
RV = residual volume
TLC = Total lung capacity
VC = Vital capacity

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Received: VIII-08-2023; accepted: VIII-18-2023.

How to cite: Vargas-Domínguez C, Vázquez-García JC. Repeatability and reproducibility of inspiratory capacity measurement by spirometry and body plethysmography. Neumol Cir Torax. 2023; 82 (1): 7-13. https://dx.doi.org/10.35366/114223

INTRODUCTION

Inspiratory Capacity (IC) is the maximum volume of air that can be inhale continuously from one point to the end of a normal exhalation (tidal volume) to a point of maximum inhalation or total lung capacity (TLC).[1,2] The initial point on inhalation of the IC corresponds to the functional residual capacity (FRC), it is a static volume which is also called end expiratory lung volume (EELV). In patients with limited expiratory airflow due to obstructive pulmonary diseases, the EELV is determined by the time constant, tidal volume and the expiratory time.[3] Changes in any of these variables that increase the EELV causes an IC decrease. This is functionally relevant because the IC represents a reserve for the tidal volume and, thus, for minute ventilation in exercise conditions.[4] IC measuring has been frequently used for investigation purposes; it can be more sensitive than the forced expiratory volume in one second (FEV1) for the quantification of the functional improvement after different therapeutic interventions in patients with chronic obstructive pulmonary disease (COPD). IC predicts dynamic hyperinflation and exercise limitations,[5-7] it correlates with syndromes such as dyspnea, bronchodilators response, and exercise tolerance.[6,8-17] IC has been use as an improvement indicator in pulmonary rehabilitation programs that involve upper and lower limbs, with or without oxygen therapy[18-20] in non-invasive mechanical ventilation[21] and in surgery of volume reduction.[22] Similarly, IC has been used to define the pulmonary hyperinflation like the relation IC/TLC below 25%. Conceptually, this indicator represents the pulmonary inspiratory fraction and has been described as an important predictor of mortality in patients with COPD.[23] IC can be measure by both vital capacity (VC) by body plethysmography. Even when the repeatability and reproducibility of the IC has not been fully explored, the standard of the American and European Societies (ATS/ERS) recommend an IC repeatability of less than 150 mL or less based on the experience of the group and following good practices.[2] The objective of this study was to describe the repeatability and reproducibility of the different IC measurement techniques, both by slow spirometry and by body plethysmography in a sample of healthy adults.

MATERIAL AND METHODS

A descriptive and prospective study with a convenience sampling was conducted, according to the availability of the laboratory of pulmonary function for the participants studies, who were healthy subjects; most of them workers of the institution, over 18 years of age, without any acute nor chronic respiratory disease history, without respiratory symptoms and without a history of active smoking (less than 400 cigarettes throughout their lives); all of them signed an informed consent form. Subjects who were unable to perform the acceptable maneuvers of forced spirometry, slow spirometry or body plethysmography were removed. Respiratory function tests were always performed in the same order (slow spirometry, forced spirometry and body plethysmography) and as indicated by the ATS/ERS 2005 standards, in force at the time of the study.[24] All the tests were performed by expert technicians from the laboratory of pulmonary function and subsequently qualified by the same observer to ensure the criterion of acceptability and repeatability was met. One equipment of respiratory function tests (MasterScreen Body, Jaeger, Hochberg, Germany) was used for all tests. The equipment was calibrated for volume with a three-liter syringe daily before the start of the day. The maximum variability accepted was ± 3%. The subjects were instructed to perform the maneuvers and later a technician demonstrated each maneuver. All subjects performed a forced spirometry, sitting down and in all a minimum of three acceptable maneuvers were obtained, for which up to eight attempts were made. The spirometry must fulfill the repeatability criterion, defined as a difference of less than 150 mL between the two highest values of force vital capacity (FVC) and the two highest values of FEV_1.

Inspiratory capacity measurement (IC). Once the subject is seated, the nasal clamp and the mouthpiece of the spirometer were placed, avoiding the presence of air leakage. The individual had to be relaxed and it was requested a normal breathing, for at least three respiratory cycles or until we obtained a stable level of FRC. Two different maneuvers have been described to measure the inspiratory capacity. Maneuver 1 is performed with an IC after reaching a stable level of FRC (no movement of FRC up or down from the level at the end of expiration), the subject should inhale rapidly to the point of TLC (maximum inspiration), followed by a relaxed maximum exhalation until reaching to residual volume (RV). In the maneuver, after obtaining a stable FRC, the subject is asked to exhale completely and in a relax way until a plateau of one second is achieved; after that it is asked to completely inhale until reaching TLC (inspiratory VC) and to exhale completely again in a relaxed way and until reaching a plateau of at least one second (expiratory VC). All subject were able to complete at least three acceptable measurements of VC for both maneuvers with a repeatability less than 150 mL.

Body Plethysmography. The participants were placed inside the cabin sitting straight, and the mouthpiece was adjusted to the appropriate height of the mouth, without bending the neck. The door of the chamber was closed and it was given enough time, usually one minute, for the temperature to equilibrate and the individual to feel comfortable. Afterwards the correct position of the mouthpiece and the nasal clamp was explained; then, it

Table 1: General characteristics of the studied population.

Variable	Men (n = 27)	Women (n = 22)	Total (n = 49)
Age, years	33.7 ± 7.3 (26-51)	35.1 ± 0.07 (27-65)	33.2 ± 8.3 (26-65)
Weight, kg	78.5 ± 10.5 (63-116)	62.5 ± 9.1 (46-82)	71.1 ± 12.8 (46-116)
Height, m	1.75 ± 0.05 (1.64-1.87)	1.59 ± 0.06 (1.49-1.81)	1.67 ± 0.10 (1.49-1.82)
BMI, kg/m^2	25.7 ± 3.1 (21.6-38.3)	24.6 ± 2.8 (20.0-30.1)	25.2 ± 3.0 (20-38.3)
*Participants with BMI ≥ 25 kg/m^2	14 (51.8%)	10 (45.5%)	24 (50.0%)
*Participants with BMI ≥ 30 kg/m^2	1 (3.7%)	1 (4.5%)	2 (4.0%)
Forced spirometry maneuver	4.4 ± 1.3 (3-8)	4.3 ± 1.5 (3-7)	4.3 ± 1.3 (3-8)
FVC, L	5.24 ± 0.65 (3.78-6.54)	3.55 ± 0.8 (2.66-4.65)	4.46 ± 1.01 (2.66-6.54)
FVC, %p	110.0 ± 12.3 (80-139)	103.9 ± 11.3 (92-128)	109.3 ± 11.9 (80-144)
FEV_1, L	4.23 ± 0.51 (3.13-5.43)	2.91 ± 0.43 (2.02-3.98)	3.62 ± 0.82 (2.02-5.43)
FEV_1, %p	105.1 ± 11.8 (79-144)	109 ± 11.9 (78-130)	104.3 ± 11.8 (79-144)
FEV_1/FVC, %	81.8 ± 5.2 (70.7-92.6)	83.3 ± 5.1 (74.1.6-92.0)	82.6 ± 5.1 (70.7-92.6)

Values are expressed in mean ± standard deviation (minimum and maximum value), and others in n (%)*.
%p = percent predicted. BMI = body mass index. FVC, forced vital capacity. FEV_1 = forced expiratory volume in the first second.

was asked to breath normally (tidal volume) until the FRC was stable, normally between three to 10 breaths. At the end of a normal tidal volume exhalation (FRC level) the obturator occluded, for two to three seconds, and it was requested to performed a series of gentle panting breaths at an approximate frequency of one breath per second. When the obturator reopened, a VC maneuver was completed; equal to the maneuver 1 of slow spirometry. An acceptable maneuver was defined by: 1) stable FRC before occlusion; 2) the difference of volume (DV) at the level of FRC at the time of the valve occlusion should be less than 200 mL; 3)both ends of the plethysmographic FRC curve (FRC_{pleth}) should be visible on the graph; 4) the respiratory rate during the obturation should be approximately 60 breaths per minute (30-90); 5) The FRC_{pleth} curve should be regular and with minimal hysteresis (the inspiration and expiration phases should be practically superimpose); 6) the slope of the measurement line should be parallel to the expiratory part of the FRC_{pleth} curve; and 7) at least, three acceptable FRC_{pleth} maneuvers should be obtain. For the VC maneuver, a plateau of at least one second without change in volume should be reached. Repeatability of the plethysmographic was calculated after obtaining three acceptable maneuvers. The FRC_{pleth} should have a variance of less than 5%. [(higher FRC_{pleth}-lower FRC_{pleth})/ average FRC_{pleth}]. Moreover, the VC must be repeatable at less than 150 mL between the two of the highest values.

Data Analysis. For the general description of the variables, averages and standard deviation (SD) or, proportions according to the type of variables. The IC variability in mL and in percentage between the two highest values of each test (spirometric and plethysmographic) was quantified as average values in mL and in percent, as well as 90 and 95 percentiles. Additionally, the coefficient of correlation (Pearson r) and graphical concordance analysis was calculated with the Bland *et al.*[25] test for the IC measurements of the spirometry and plethysmography.

RESULTS

A total of 56 participants were included, four subjects who could not perform acceptable forced spirometry maneuvers, two other subjects by IC maneuver 2 and one by plethysmography were eliminated, so the final sample was 49 participants, 27 men and 22 women, with an average age of 33.2 ± 8.3 years (26 to 65 years). *Table 1* shows the general, anthropometric characteristics and forced spirometry results of the population studied. Overall, all presented FVC, FEV_1 and FEV_1/FVC ratio values within baseline limits.

Table 2 shows the repeatability of IC maneuvers performed by slow spirometry and by body plethysmography. The total number of maneuvers performed to obtain a minimum of three acceptable efforts were on average 4.5 ± 1.0 (three to eight efforts) for IC maneuver 1 and 4.5 ± 0.9 (three to eight) for maneuver 2; for plethysmography 5.0 ± 1.1 (three to seven efforts) were performed. In addition, the repeatability values of each test are shown as averages, percentages, and 90 and 95 percentiles (p90, p95). The repeatability of IC was ≤ 150 mL in 96% of participants or ≤ 5% in 98%

of subjects for spirometry maneuvers 1 and 2, while for plethysmography it was 78 and 80%, respectively.

Figures 1 to 2 show the correlation graphs and Bland and Altman graphical analysis of IC between spirometry maneuvers 1 and 2 *(Figure 1)*, as well as maneuvers 1 and 2 versus plethysmography *(Figure 2)*. The CI values with the three measurements were highly correlated (Pearson r) with a correlation coefficient of 0.95 between maneuvers 1 and 2; 0.87 between maneuver 1 and plethysmography, as well as 0.88 between maneuver 2 and plethysmography). However, concordance between measurements (Bland and Altman analysis) showed potential errors of up to 576 mL between maneuvers 1 and 2, 954 mL (maneuver

Table 2: Repeatability of the inspiratory capacity tests.

	Inspiratory Capacity (IC)		
Parameter	**Maneuver 1**	**Maneuver 2**	**Plethismography**
Number of maneuvers	4.5 ± 1.0 (3 to 8)	4.5 ± 0.9 (3 to 8)	5.0 ± 1.1 (3 to 7)
Average IC, L	3.12 ± 0.78 (2.03-5.24)	3.17 ± 0.74 (2.11-5.32)	3.15 ± 0.95 (1.09-5.76)
Repeatability in mL Percentile 90, mL Percentile 95, mL	69.0 ± 68.1 (0-420) 122 150	72.3 ± 50.2 (0 a 210) 130 146	108.5 ± 100.0 (0 a 420) 244 318
≤ 100 mL, n (%) ≤ 150 mL, n (%) ≤ 200 mL, n (%)	38 (77.6) 47 (95.9) 48 (98.0)	35 (71.4) 47 (95.9) 48 (98.0)	28 (57.1) 38 (77.6) 41 (83.7)
Repeatability in %	2.3 ± 2.5 (0-15.3)	2.4 ± 1.8 (0-7.4)	3.4 ± 3.2 (0-10.8)
≤ 3 % mL, n (%) ≤ 5 % mL, n (%) ≤ 10 % mL, n (%)	22 (44.8) 48 (98.0) 49 (100)	20 (40.8) 48 (98.0) 49 (100)	30 (61.2) 39 (79.6) 45 (91.8)

Except when otherwise noted, values are expressed in mean ± standard deviation (minimum and maximum value).

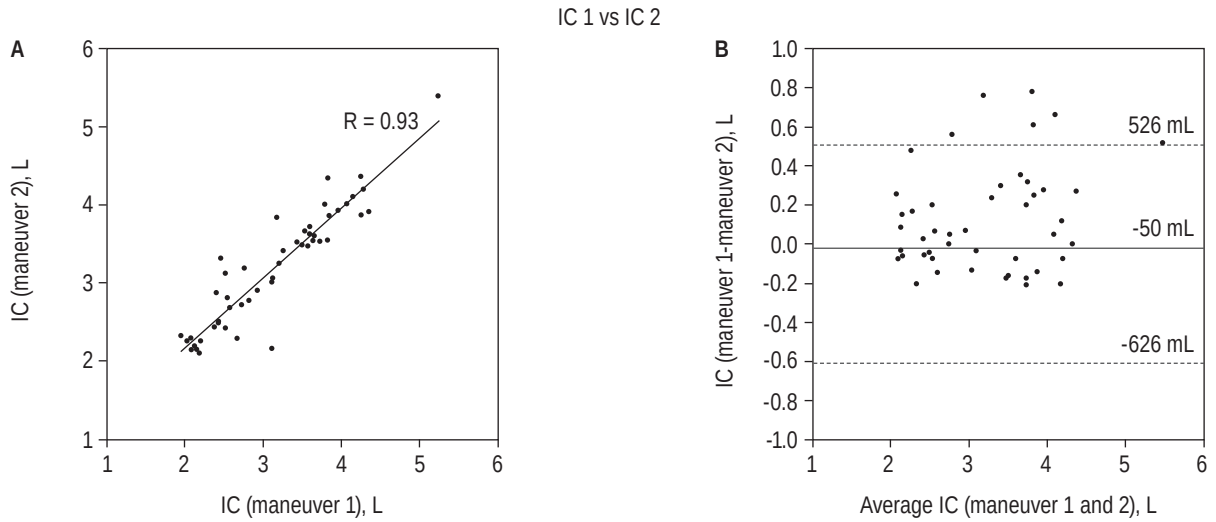

Figure 1: Graph **A** presents the correlation between inspiratory capacity (IC) measurements measured by slow spirometry. Maneuver 1 or IC 1 corresponds to the CI measured posterior to tidal volume (onset from residual functional capacity) and maneuver 2 (IC2) corresponds to the measurement with inspiratory vital capacity maneuver followed by expiratory vital capacity. Graph **B** shows the agreement analysis of Bland and Altman; the average of both measurements (IC1 and IC2) is plotted against the difference between the two. This analysis summarizes the potential differences or errors between both measurements which, in this case, is -50 ± 576 mL (average and two standard deviations).
IC = inspiratory capacity. L = liters

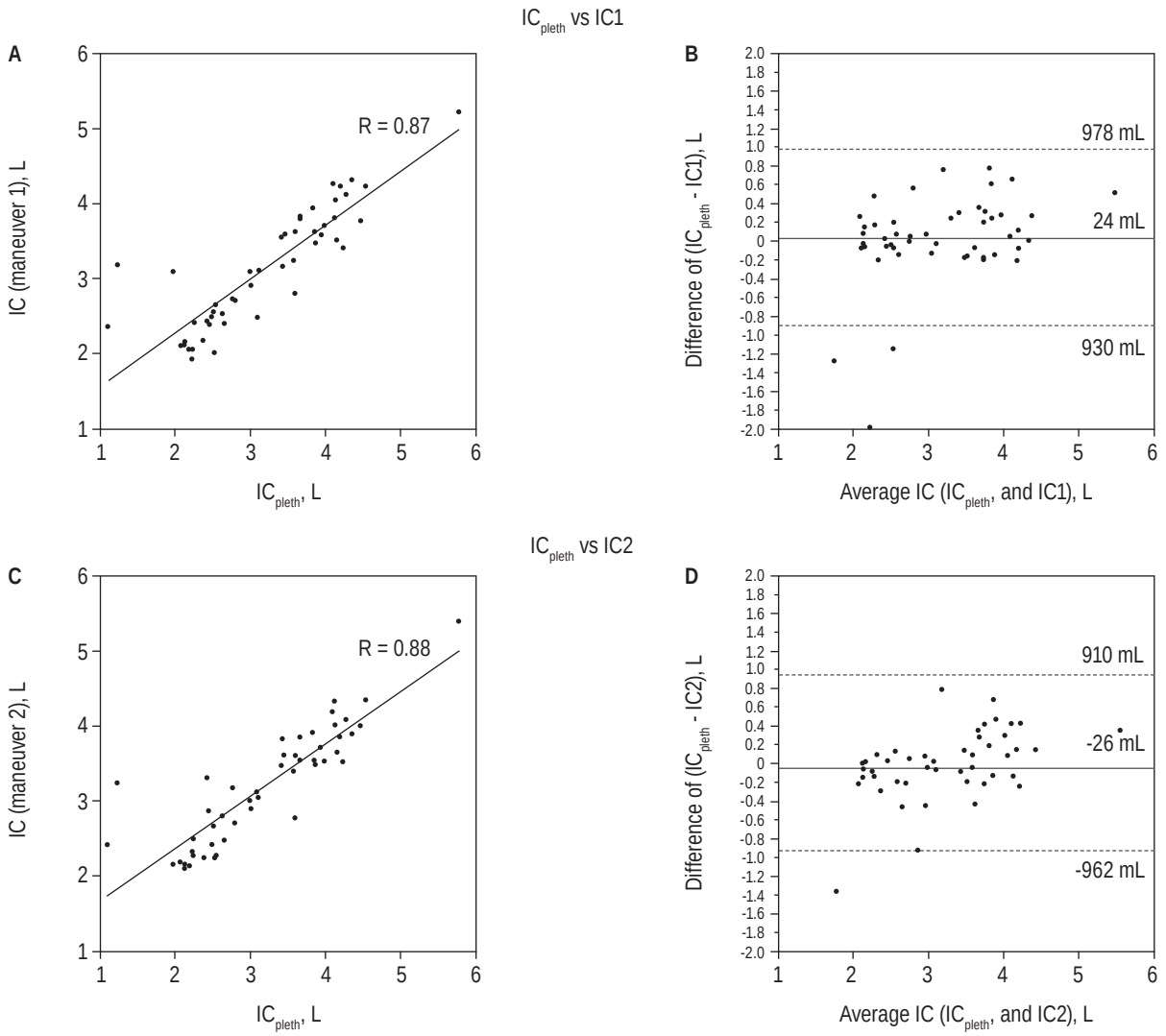

Figure 2: In the upper panel in graph **A**, the correlation between inspiratory capacity measurements measured by plethysmography (IC_{pleth}) compared to slow spirometry maneuver 1 (IC1) is shown. Graph **B** shows the concordance analysis (Bland and Altman); the average of both measurements (IC_{pleth} and IC1) is plotted against the difference between the two, the difference or error is 24 ± 954 mL (average and two standard deviations). In the lower panel in graph **C** the correlation is shown and in graph **D** the concordance between IC_{pleth} and slow spirometry maneuver 2 (-26 ± 936 mL).
L = liter.

1 versus plethysmography), and 936 mL (maneuver 2 versus plethysmography.

DISCUSSION

This study explores technical aspects and variability of IC measurement in healthy subjects, both measured by slow spirometry and by body plethysmography. The most relevant results were: 1) the vast majority of subjects were able to perform acceptable maneuvers in all tests; 2) spirometry maneuvers were more repeatable than plethysmography; and 3) in general, all IC measurements had a high correlation; however, in the concordance analysis, potential differences close to a liter are revealed when spirometry is compared with plethysmography.

Initially, the variability of the IC maneuvers obtained by slow spirometry (maneuvers 1 and 2) corresponding to the measurement of IC from FRC (maneuver 1) and measurement of IC subsequent to an inspiratory vital capacity (maneuver 2) was explored, which allowed evaluating the interchange ability of the maneuvers. Both showed similar performance based on the number of maneuvers required to achieve an acceptable test and repeatability values. The criteria for acceptability of IC are those of the slow VC maneuver already described.[2] However, the repeatability that can be achieved between

maneuvers for IC has not been fully explored. Tantucci *et al*.[26] reported repeatability of 200 mL or less (< 9%) in 241 healthy subjects aged 65 to 85 years. As in any respiratory function test, it depends on the accuracy and precision of the equipment, the required respiratory maneuver, the ability of the technician and the cooperation of the people undergoing the test, as well as their interaction with the technician. Forced spirometry and slow spirometry are known to achieve high repeatability of FEV_1, FVC and VC, so repeatability of IC could be expected to be high as well. International spirometry standards ATS/ERS 2019 require repeatability of less than 150 mL for all these values. However, this value is defined based on the experience of the working group and good practices. In this study, for both slow spirometry IC maneuvers, 96% of subjects achieved repeatability of 150 mL or less and in 98% it was ≤ 5%. Consequently, it can be affirmed that any of the spirometric values (FEV_1, FVC, VC and IC) are technically very reliable for the purposes of diagnosis, monitoring and measurement of change; as is the case in the bronchodilator response test, in the monitoring of respiratory patients or in people exposed to respiratory risks, as well as in the evaluation of therapeutic interventions.

Another finding of this study is that IC measurements by spirometry achieved better repeatability than plethysmography. The IC measured by plethysmography showed higher repeatability values and with potential differences of almost one liter *(Figure 2)*. This could be explained because the IC maneuver performed by plethysmography is technically more complex and requires greater training and cooperation, as it is done sequentially with the measurement of residual functional capacity (FRC_{pleth}). Plethysmography requires a period in which there is an occlusion of the nozzle obturator (two to three seconds) where the FRC_{pleth} is measured and after that the IC maneuver is performed. In contrast, with slow spirometry, the IC maneuver is performed after a tidal volume expiration. CI values had a good correlation between slow spirometry and plethysmography measurements *(Figures 1 and 2)*. This means that the maneuvers are not completely interchangeable and for follow-up purposes the same test should always be considered, preferably by slow spirometry. The main limitation of this study is that it explores a limited number of healthy subjects and sampling of the studied population was for convenience, which might not be fully representative of the general population or patients with respiratory diseases.

CONCLUSIONS

The measurement of IC, mainly when measured by slow spirometry and with any of the accepted maneuvers, showed acceptability and repeatability of 150 mL or less in 96% of the subjects; while for plethysmography it was in 78% of the participants. Overall, all IC measurements had a high correlation coefficient. However, concordance analyses reveal potential differences close to a liter when compared to plethysmographic measurements, so they should not be considered interchangeable. This study supports the current ATS/ERS 2019 spirometry standards recommendation of requiring a repeatability of 150 mL or less for IC measurement.

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Conflict of interests: the authors declare that they have no conflict of interests.

NCT
Neumología y Cirugía de Tórax
Vol. 82 - No. 1 / January-March 2023

Original
doi: 10.35366/114224

Sex-associated differences in pulmonary disease caused by mycobacteria diagnosed at INER from 2016-2018

Diferencias por sexo en enfermedad pulmonar causada por micobacterias diagnosticada en el INER en el período 2016-2018

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ABSTRACT. Introduction: pulmonary tuberculosis affects men more frequently and severely. Whether this phenomenon occurs similarly for the non-tuberculous mycobacteria remains unknown. **Objective:** we aimed to identify if there is sex predominance in pulmonary diseases caused by *Mycobacterium tuberculosis* and other mycobacteria. **Material and methods:** we performed a retrospective cross-sectional study. We studied cases of pulmonary disease in adults with a positive culture for any mycobacteria during 216-2018 at INER. We included 553 cases. **Results:** the main mycobacteria that we found belonged to the *Mycobacterium tuberculosis* complex (73.42%), *M. avium* complex (16.64%), and other non-tuberculous mycobacteria (9.95%). Most cases were men in general (60.58%), and in the three groups, *Mycobacterium tuberculosis* complex (56.40%), *M. avium* complex (75%), and other non-tuberculous mycobacteria (62.79%). The main comorbidities were HIV infection for men and diabetes mellitus for women. **Conclusions:** men were mainly affected with pulmonary mycobacteriosis, *Mycobacterium tuberculosis,* and other non-tuberculous mycobacteria. This phenomenon poses changes in clinical approaches and the search for intrinsic determinants of men's susceptibility to these infections.

Keywords: mycobacteria, pulmonary disease, tuberculosis, non-tuberculous mycobacteria.

RESUMEN. Introducción: la tuberculosis pulmonar afecta con mayor frecuencia y en formas más severas a los hombres. Se desconoce si este fenómeno se replica en la enfermedad pulmonar causada por otras micobacterias. **Objetivo:** identificar si existe predominancia de un sexo en la enfermedad pulmonar causada por *Mycobacterium tuberculosis* y otras micobacterias. **Material y métodos:** estudio retrospectivo transversal que consistió en realizar la revisión de casos con enfermedad pulmonar en adultos con cultivo positivo para cualquier micobacteria durante los años 2016 a 2018 en el Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas de la Ciudad de México. Se incluyeron un total de 553 pacientes. **Resultados:** las principales micobacterias encontradas fueron del complejo *Mycobacterium tuberculosis* (73.42%), complejo *M. avium* (16.64%) y otras micobacterias no tuberculosas (9.95%). La mayoría de los casos fueron hombres en general (60.58%) y en los tres grupos, complejo *Mycobacterium tuberculosis* (56.40%), complejo *M. avium* (75%) y otras micobacterias no tuberculosas (62.79%). La principal comorbilidad de los hombres fue la infección por el virus de la inmunodeficiencia humana, y en las mujeres fue la diabetes *mellitus*. **Conclusiones:** los hombres fueron principalmente afectados con infecciones pulmonares causadas por micobacterias, tanto *Mycobacterium tuberculosis* como por las otras micobacterias no tuberculosas. Este fenómeno sugiere cambios en el manejo clínico y la búsqueda de los determinantes intrínsecos de la susceptibilidad de los hombres.

Palabras clave: micobacterias, enfermedad pulmonar, tuberculosis, micobacterias no tuberculosas.

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Received: V-02-2023; accepted: IX-11-2023.

How to cite: Sartillo-Mendoza LG, Martínez-Sanabria CA, Becerril-Vargas E, González Y, Juárez E. Sex-associated differences in pulmonary disease caused by mycobacteria diagnosed at INER from 2016-2018. Neumol Cir Torax. 2023; 82 (1): 14-20. https://dx.doi.org/10.35366/114224

INTRODUCTION

Pulmonary tuberculosis, mainly caused by *Mycobacterium tuberculosis* (*M. tuberculosis*), is the second leading cause of death associated with a single pathogen in the world. In 2021, men accounted for 56%, women 32% and children12% of new global cases; in addition, 53% of deaths recorded during 2021 occurred in men, 31% in women and16% in children.[1] Men, on the other hand, are more susceptible than women to developing severe forms with greater lung damage, have greater need for retreatment, more co-infections and, in some countries with high incidence, are more susceptible to developing drug resistance.[2-4]

Non-tuberculous mycobacterial lung disease (NTM) presents with a clinical picture similar to that of tuberculosis and can be caused by a variety of mycobacterial species.[5] This disease is geographically diverse and the existing data are heterogeneous due to the lack of national coverage reports, but, in general, it is accepted that the majority of cases occur by species members of the *M. avium* complex (*M. avium* and *M. intracellulare*).[6] In the United States and Canada, the majority of cases occur in women (86% and 61%, respectively), although population-based studies are not reported, nor is an association of sex and age with mortality reported.[7,8]

The predominance of either sex in tuberculosis and mycobacterial lung disease could have an effect on clinical practice, follow-up of cases to prevent complications, and personalized supervision of drug therapy. In addition, the difference between the sexes makes it necessary to implement new clinical and basic research protocols for the identification of socioeconomic and immunological determinants of susceptibility. Therefore, this work aims to identify whether there is a predominance of one sex in lung disease caused by *M. tuberculosis* and other mycobacteria in a third-level Mexican hospital.

MATERIAL AND METHODS

Description of the study and origin of the data. This study is a retrospective case series. It consisted of searching for cases with lung disease that have tested positive for any mycobacteria during the years 2016 to 2018 in the archives of the Clinical Microbiology Service of the National Institute of Respiratory Diseases Ismael Cosío Villegas (INER) of Mexico City. The study was approved by the INER science and research ethics committees (code C56-22) with a waiver of the letter of informed consent by virtue of the fact that the research was retrospective, the confidentiality of the information was ensured and the personal identification of the patients was eliminated.

Selection of the study sample. In the file of the Clinical Microbiology Service, 2,068 case records with positive culture for any mycobacteria were found. All patients whose samples were of pulmonary origin such as expectoration, bronchoalveolar lavage, lung biopsy and bronchial aspirate from individuals over 18 years of age who had a record in the INER were selected for this study. A total of 553 patients were included *(Figure 1)*. For the analysis of comorbidities, a random selection of 165 files was made, 81 men and 84 women. The number of positive cases for the different complexes was taken into account in the calculation of the sample size of each group.

Statistic analysis. The number of individuals with lung disease caused by the different mycobacteria is presented as number of individuals or percentage. These data are shown in tables or proportion graphs and are only described, no statistical tests were performed. To establish the differences in continuous variables in the different types of mycobacteria, the Kruskal-Wallis test was performed, followed by the Dunn test for comparisons of pairs of samples. Categorical variables are presented in tables. Men and women were compared for each type of mycobacterium using Fisher's exact test. In all cases, $p < 0.05$ was considered significant and the GraphPad Prism ver 9 software (La Joya, CA, USA) was used.

RESULTS

Mycobacteria found in samples of respiratory origin in adults. This study was conducted retrospectively covering the years 2016, 2017 and 2018. The samples used for diagnosis were expectoration (50.63%), bronchoalveolar lavage (31.1%) and lung biopsy (18.26%). *M. tuberculosis* is the mycobacterium that occurred in the largest number of cases in samples of respiratory origin *(Table 1)*. Mycobacteria *M. avium, M. bovis and M. intracellulare* were the mycobacteria other than *M. tuberculosis* that were found in the highest number of cases. Other mycobacteria occurred less frequently.

Distribution by sex of mycobacterium species reported in the study period. Pulmonary tuberculosis was the main pulmonary disease caused by a mycobacterium (67% of cases); the next in frequency were *M. avium, M. bovis and M. intracellulare* (among the three represent 22.61%), and the other mycobacteria represent 9.95% *(Figure 2A and 2B)*. 60.58% of patients were male *(Figure 2C)* and these comprise the largest number of cases with *M. tuberculosis* and with any other mycobacterium *(Figure 2D)*. Because *M. tuberculosis* and *M. bovis* belong to the *M. tuberculosis* complex (*M. tuberculosis* complex: *M. tuberculosis*, *M. bovis, M. africanum, M. canetti, M.microtti*) and *M. avium* and *M. intracellulare* belong to the *M. avium* complex, the data were grouped into three categories, the *M. tuberculosis* complex, *M. avium* complex and other mycobacteria. The highest number of cases are men in the three groups, *M.*

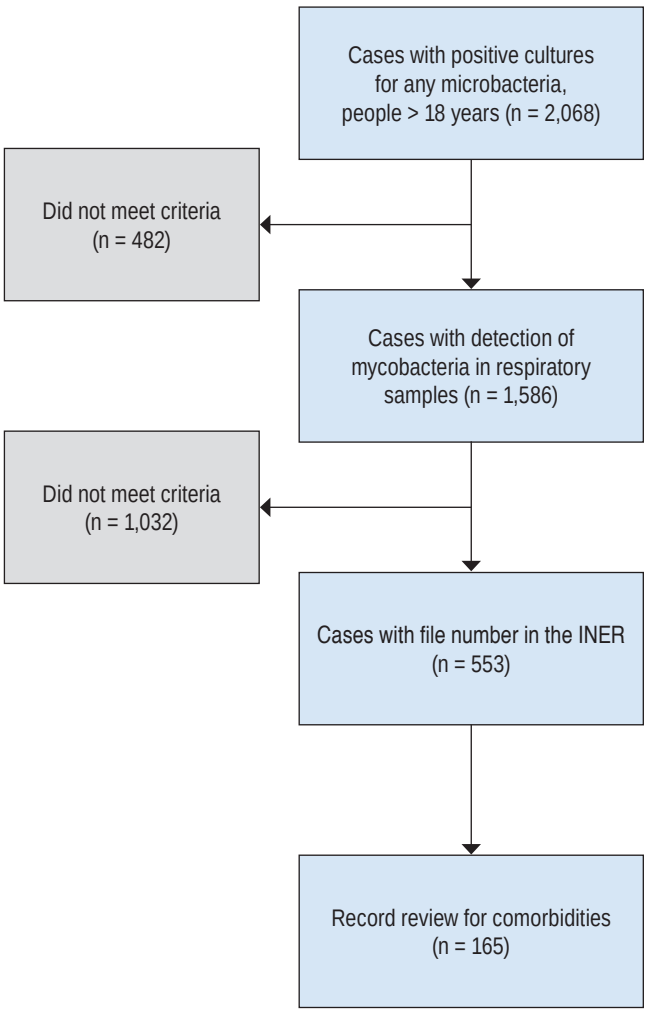

Figure 1: Selection of the study sample.

tuberculosis complex (56.40%), *M. avium* complex (75%) and other NTM (62.79%) *(Figure 2E and 2F)*.

Additionally, we observed that the majority of patients were younger than 60 years of age *(Figure 3A)*, and the pattern is preserved when separated by mycobacterial complex *(Figure 3B)*. There was no difference in the ages of men and women infected by members of the *M. tuberculosis* complex. In the male group, patients infected by members of the *M. avium* complex were significantly younger than those infected by *M. tuberculosis* and other MNT, but there was no difference between the latter two *(Figure 3C)*. Women who became infected with members of the *M. avium* complex and other NTM were significantly older than those who became infected with members of the *M. tuberculosis* complex *(Figure 3D)*.

Main comorbidities observed in men and women with lung disease caused by mycobacteria. To determine the relevance of comorbidities, 81 men and 84 women were randomly selected and analyzed by group *(Table 2)*. The proportion of patients with human immunodeficiency virus (HIV) was significantly higher in men infected with members of the *M. tuberculosis* and *M. avium* complexes, but not in the other NTM; this directly influenced the overall. The proportion of women with hypertension was significantly higher in patients infected with members of the *M. avium* complex. There were no differences between men and women, in either group, in the proportion of individuals with diabetes mellitus or cancer.

DISCUSSION

Mycobacterial infections are a growing global health problem. Both *M. tuberculosis* and NTM infection are often seen in people who have a compromised immune system, which not only makes infection permissible, but also favors the development of active lung disease.[9,10] In this study we investigated the prevalence of the different species of mycobacteria in patients who come with lung disease

Table 1: Species of mycobacteria found in samples of respiratory origin between 2016 and 2018 in the INER.

	Number of cases			
Species	**2016**	**2017**	**2018**	**Total**
M. tuberculosis	99	127	147	373
M. avium	17	22	22	61
M. bovis	7	9	17	33
M. intracellulare	12	11	8	31
M. abscessus	2	6	7	15
M. chelonae	3	2	3	8
M. fortuitum	1	1	4	6
M. gordonae	1	3	2	6
M. simiae	1	3	2	6
M. kansasii	0	3	1	4
M. genavense	0	1	1	2
M. mucogenicum	0	1	1	2
M. szulgai / M. lentiflavum	0	0	1	1
M. malmoense	0	0	1	1
M. bovis / M. chelonae	0	0	1	1
M. tuberculosis / M. chelonae	0	1	0	1
M. scrofulaceum	1	0	0	1
M. xenopi	1	0	0	1
Total				553

with suspected tuberculosis to a Third Level Respiratory Disease Hospital, the INER, who had a positive culture for any species of mycobacteria, and identified whether there is a predominance of one sex in lung disease caused by mycobacteria.

We observed that the lung disease under study was mainly caused by *M. tuberculosis*. This infection occurred more frequently in men under 60 years of age and was associated with a greater number of comorbidities, the main one being diabetes mellitus. These data are consistent with other studies, in which a higher prevalence has been reported in men.[11,12] The most frequent NTMs included mycobacteria of the *M. avium* and *M. bovis* complex, which are part of the *M. tuberculosis* complex. For this reason, we divided the groups into those infected by members of the two complexes and by other NTM.

Mycobacterial infections of the *M. avium* complex, which includes *M. intracellulare*, are the most common NTM found in our study group. These data are also consistent with what was recorded in other populations.[10,13,14] Contrary to expectations, we also observed this infection predominantly in men. Unlike infections by members of the *M. tuberculosis* complex, we detect that infection caused by members of the *M. avium* complex is more

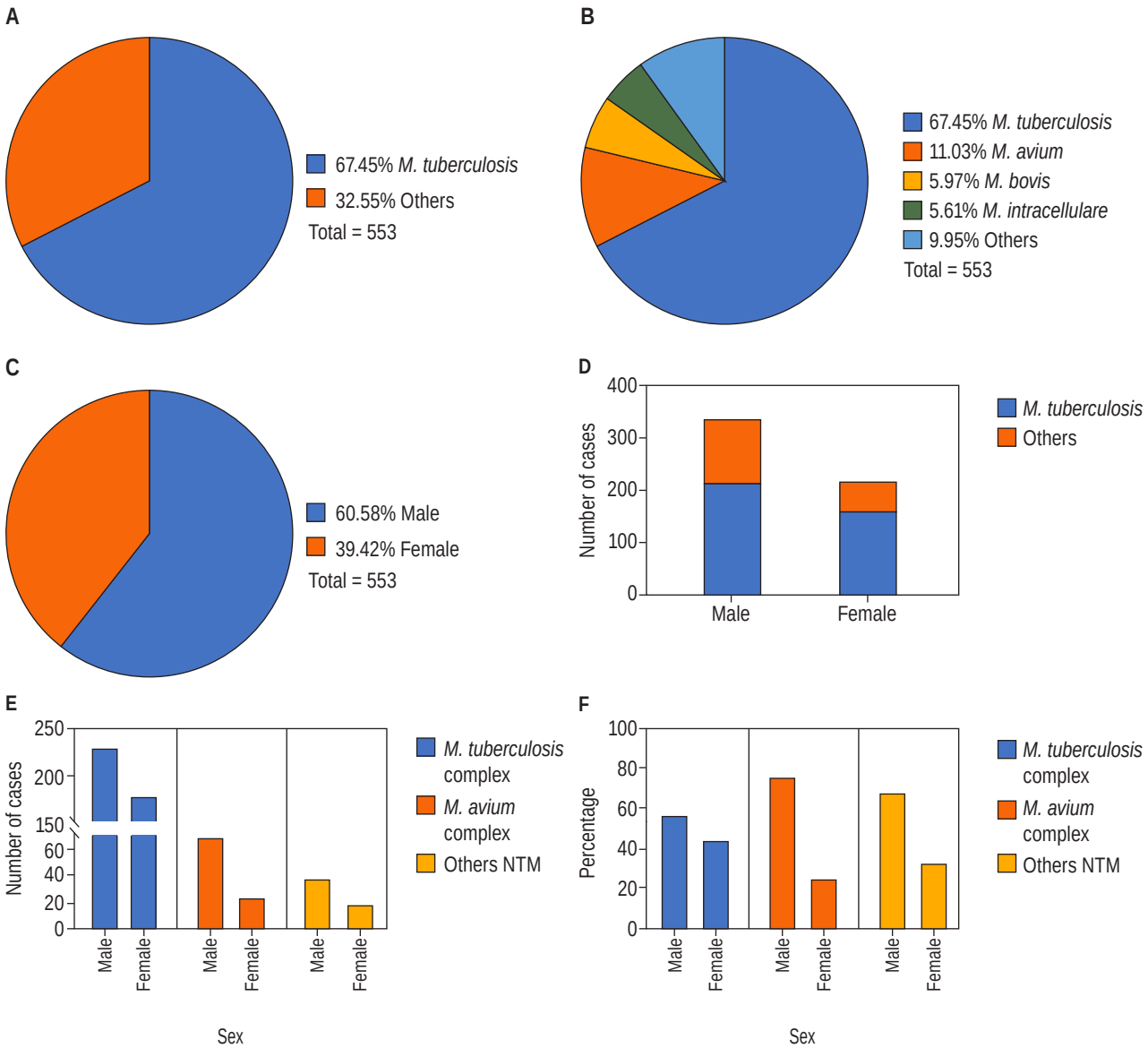

Figure 2: Distribution by sex of cases with lung disease caused by mycobacteria. **A and B)** Main species of mycobacteria found in samples of respiratory origin. **C and D)** Distribution by sex in the total sample, N = 553, and **E and F)** by groups of individuals infected with bacteria of the *M. tuberculosis* complex, *M. avium* complex and other mycobacteria. NTM= Non-tuberculous mycobacteria.

Contenido

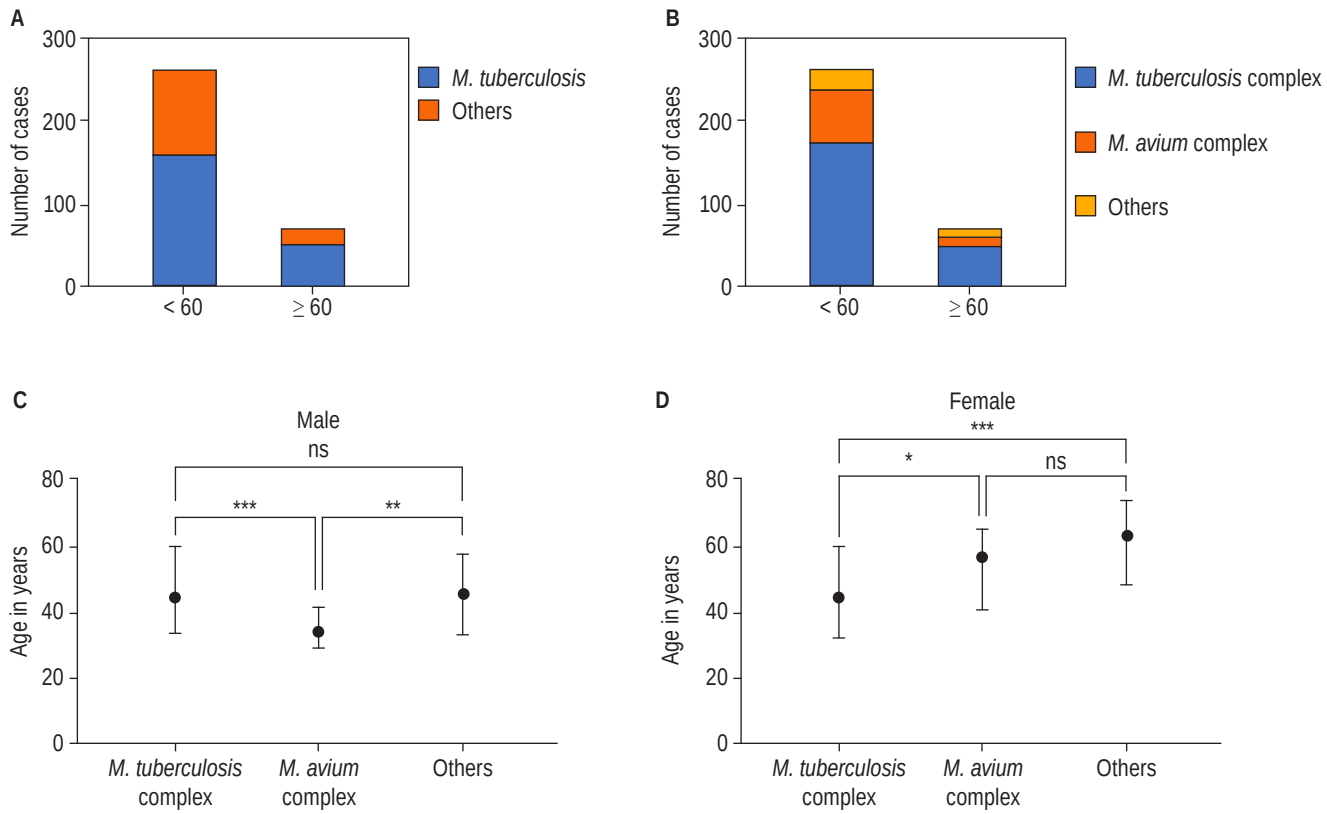

Figure 3: Distribution of lung disease caused by mycobacteria in older and younger than 60 years. **A and B)** Number of cases that occur in people over or under 60 years of age. **C and D)** Age of men and women with infection by bacteria of the *M. tuberculosis* complex, *M. avium* complex and other mycobacteria. Medians with interquartile range are shown, N = 553; *p < 0.05, **p < 0.01, ***p < 0.001, Kruskal-Wallis ANOVA followed by Dunn's test.

Table 2: Proportion of patients* with comorbidities by group.

Characteristics	*M. tuberculosis* complex		*M. avium* complex		Others		Total	
Sex	Male n = 55	Female n = 66	Male n = 19	Female n = 10	Male n =7	Female n = 8	Male n = 81	Female n = 84
Age, years, median (range)	36.5 (20-85)	34.5 (18-88)	34 (21-54)	56.4 (22-77)	55 (28-65)	60 (39-74)	45 (20-85)	45 (18-88)
HIV‡	12 (21.8)§	3 (4.5)	15 (78.94)¶	2 (20)	4 (36.3)	0 (0)	31 (38.3)¶	5 (6)
Cancer‡	0 (0)	2 (3.03)	1 (5.26)	0 (0)	0 (0)	0 (0)	1 (0.12)	2 (2.4)
Diabetes mellitus‡	21 (38.1)	25 (37.8)	0 (0)	3 (30)	0 (0)	2 (25)	21 (26)	30 (35.7)
Hypertension‡	8 (14.5)	10 (15.1)	0 (0)	5 (50)§	0 (0)	2 (25)	8 (9.9)	17 (20.2)
Others (exposure to wood smoke, smoking, drug use)	21 (38.2)§	9 (13.6)	5 (26.3)§	0 (0)	6 (85.7)	5 (62.5)	32 (39.5)‖	14 (16.7)

* Random selection of a sample of 81 men and 84 women. ‡ «Yes», frequency and percentage [n (%)]. § p > 0.05. ¶ p < 0.001. Fisher's exact test ‖ p < 0.01.

frequent in people under 35 years of age, perhaps associated with HIV infection. In other populations it has been recognized that *M. avium* infection occurs mainly in people over 65 years of age.[13] This phenomenon is only observed in women. We also observed that the prevalence of M. avium in people living with HIV is higher than that reported in other populations,[15] so *M. avium* monitoring is required in this specific group of patients.

Unlike reports of *M. tuberculosis* infections, which occur similarly in most populations, the prevalence of infections by members of the *M. avium* complex depends on the populations studied.[16] We observed that infection by members of the *M. avium* complex in the group of women occurs in older than 60 years, with hypertension and diabetes mellitus as the main comorbidities. There are no reports of association between *M. avium* infection and hypertension, although *M. avium* has been reported concomitantly with acute kidney disease as a rare clinical event.[17] Additionally , susceptibility to *M. avium* infection has been reported in postmenopausal women with low levels of dehydroepiandrosterone sulfate (DHEA-S), without alterations in estrogen levels (estradiol and estrone);[18] but other reports suggest that this susceptibility is associated with low levels of estradiol (E2), without alterations in DHEA-S,[19] so more studies are required to elucidate the role of hormones in susceptibility to *M. avium* infection in women.

We also observed that infections with other NTM such as *M. abscessus, M. chelonae, M. fortuitum, M. gordonae* and *M. simiae* occurred more frequently in men under 60 years of age. Contrary to what has been reported in other countries, these infections were less frequent in women and occurred mainly in those over 50 years of age. Although not significantly, these NTM occurred in people with exposure to wood smoke, smoking, or drug use.

Some immune functions are associated with sex. For example, steroid hormones influence the production, maturation, differentiation, and function of immune system cells and molecules.[20] Estradiol and progesterone decrease the expression of proinflammatory cytokines, such as IL-1β, IL-6, IL-2,TNF-α , and IFN-γ , and influence the production of lipid mediators of inflammation resolution.[21-23] On the other hand, the X chromosome has genes associated with the regulation of the immune response, such as those encoding IL-2, TLR7, TLR8, IL-1, IRAK1, the IL-3 and IL-13 receptor alpha chain, and several small RNAs (miRNAs) regulating the immune response, while the Y chromosome has none.[21,24,25] These features likely promote less severe clinical pictures in women. Future research will determine the contribution of these factors to mycobacteriosis.

This study has limitations mainly related to bias in the selection of samples. First, the INER is a National Institute of Health, a Third Level Hospital that mainly treats complicated or severe lung diseases. Second, because this is a retrospective study, the universe of samples that were evaluated were only those cases in which there was a clinical record in the INER. However, the result is relevant to propose additional analyses, epidemiological studies and new protocols for personalized care.

CONCLUSIONS

In a Third Level Care Center, men are mainly affected with lung infections caused by mycobacteria, both *M. tuberculosis* and the other NTM. There are currently no treatment policies that consider the predominance of men in pulmonary mycobacteriosis. Due to its impact on personalized medicine, the search for biomarkers and the follow-up of treatment, it is necessary to evaluate the phenomenon at the national level, and find out what are the social and biological factors that determine it.

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Conflict of interests: the authors declare that they have no conflict of interests.

NCT
Neumología y Cirugía de Tórax
Vol. 82 - No. 1 / January-March 2023

Review
doi: 10.35366/114225

Pulmonary stereology in chronic obstructive pulmonary disease: pulmonary functional imaging examination

Estereología pulmonar en enfermedad pulmonar obstructiva crónica: exploración funcional pulmonar por imagen

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ABSTRACT. Computed tomography images are increasingly used in order to characterize lung diseases more accurately. A good correlation with lung function has been described, especially in chronic obstructive pulmonary disease. Spirometry is currently the gold standard for chronic obstructive pulmonary disease diagnosis, but computed tomography has been positioned to identify early disease and to identify progression in established disease. In the last decade, the functional evaluation of chronic obstructive pulmonary disease by computer tomography has improved diagnostic certainty, evaluation and prediction of progression. Moreover, it allows selecting patients for therapeutic interventions. Multiple metrics are used as prognostic-related imaging biomarkers in chronic obstructive pulmonary disease and have been correlated with respiratory function tests. This review aims to analyze the current and future role of CT in COPD.

Keywords: stereology, chronic obstructive pulmonary disease, spirometry, computed tomography.

RESUMEN. Las imágenes obtenidas por tomografía computarizada se utilizan cada vez más para caracterizar con mayor precisión las enfermedades pulmonares. Se ha descrito una buena correlación con la función pulmonar, especialmente en la enfermedad pulmonar obstructiva crónica. Actualmente, la espirometría es el estándar de referencia en el diagnóstico de la enfermedad pulmonar obstructiva crónica, pero la tomografía computarizada se ha posicionado como método de imagen para identificar enfermedad temprana y progresión en enfermedad establecida. En la última década la evaluación funcional de la enfermedad pulmonar obstructiva crónica por tomografía computarizada ha permitido incrementar la certeza diagnóstica, la evaluación y la predicción de la progresión de la enfermedad. Además, proporciona una mejor selección de pacientes para intervenciones terapéuticas. Múltiples métricas de tomografía computarizada se usan como biomarcadores de imagen en la enfermedad pulmonar obstructiva crónica relacionadas con el pronóstico y se han correlacionado con las pruebas de función respiratoria. La presente revisión pretende analizar el papel actual y futuro de la tomografía computarizada en la evaluación de la enfermedad pulmonar obstructiva crónica.

Palabras clave: estereología, enfermedad pulmonar obstructiva crónica, espirometría, tomografía computada.

Abbreviations:

CT = computed tomography.
COPD = chronic obstructive pulmonary disease.
PFT = pulmonary function test.
DLco = Diffusing capacity of the lungs for carbon monoxide.
6MW = 6-minute walk.
IOS = impulse oscillometry.
IC = inspiratory capacity.
IRV = inspiratory reserve volume.
TLC = total lung capacity.
RV = residual volume.
AV = alveolar volume.
KCO = exponential decay constant of the fractional concentration of CO in an apnea time.
Rrs = resistance of the respiratory system.

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Received: VIII-11-2023; accepted: IX-14-2023.

How to cite: Hernández-Morales AP, Robles-Hernández RE, Vázquez-García JC. Pulmonary stereology in chronic obstructive pulmonary disease: pulmonary functional imaging examination. Neumol Cir Torax. 2023; 82 (1): 21-28. https://dx.doi.org/10.35366/114225

Xrs = respiratory system reactance.
HU = Hounsfield units.
QCT = quantitative computed tomography.
FEV_1/FVC = forced expiratory volume of the first second/forced vital capacity.
FEV_3 = forced expiratory volume in 3 seconds.
FEV_6 = forced expiratory volume in 6 seconds.
%WA = percentage of wall area.
RVC = relative volume change.
MRI = magnetic resonance imaging.
PBF = mean pulmonary blood flow.
PBV = pulmonary blood volume.
MTT = mean transit time.
ADC = apparent diffusion coefficient.
PET = positron emission tomography.
R5 = total airway resistance.
R20 = central area track resistance.
XA = reactance area.
Rfreq = resonant frequency.

INTRODUCTION

In middle-income countries, a prevalence of chronic obstructive pulmonary disease (COPD) of 8 to 13% has been described among adults aged 30 to 79 years and older.[1] The Latin American Project for Research on Chronic Obstructive Pulmonary Disease (PLATINO) described a prevalence of COPD of 7.8 to 20.0%, more frequent in men and at older ages, as well as in people with low educational level, low body mass index and exposed mainly to tobacco. Worldwide, there is a wide variation in diagnosis, with 10-95% underdiagnosis and 5-60% overdiagnosis.[2] By 2030, it will be the seventh leading cause of disability-adjusted life years (DALYs) worldwide. Costs attributable to the disease are primarily associated with the number of exacerbations; in the United States, the direct costs of COPD are estimated at $50 billion in direct health care expenditures.[3]

COPD is a complex and heterogeneous condition, characterized by chronic and irreversible obstruction to expiratory airflow, due to the combination of airway remodeling and pulmonary emphysema. The genesis of the disease is influenced by genetic factors, such as hereditary alpha-1 antitrypsin deficiency, matrix metalloprotease deficiencies, childhood disadvantage factors, as well as exposure to occupational, atmospheric or indoor pollutants.[4]

The evaluation and follow-up of COPD is done both by clinical parameters and by respiratory function tests (RFTs). Recently, the improvement in the quality of tomographic imaging and in the quantification of volumetric parameters related to emphysema and airway damage allow a better complementary assessment, which can be used for early diagnosis and follow-up purposes. The present review aims to describe the current status of information related to functional imaging and RFTs, as well as their future prospects for clinical use in the characterization of COPD.

DIAGNOSIS AND FUNCTIONAL ASSESSMENT OF COPD

The current diagnosis of COPD is considered a construct that integrates causes or risk factors, persistent respiratory symptoms and the presence of non-reversible airflow obstruction defined by a ratio < 0.7 between forced expiratory volume and forced vital capacity (FEV_1 and FVC).[5,6] However, these criteria may be modified in the future; several cohorts of patients who do not meet the definition of obstruction show loss of lung function and associated increased morbidity.[7]

While spirometry describes airflow limitation, additional RFTs can be incorporated, such as measurement of: static volumes by plethysmography, diffusing capacity of the lungs for carbon monoxide (DLco), six-minute walk (6MW) and impulse oscillometry (IOS), which can be useful in staging the disease and tailoring medical treatment to the needs of a heterogeneous population. Plethysmography can demonstrate air trapping and pulmonary hyperinflation, manifested by reduced inspiratory capacity (IC) and inspiratory reserve volume (IRV) with increased total lung capacity (TLC) and residual volume (RV). These indicators define pulmonary hyperinflation and air trapping, the loss of elastic recoil and the load to be broken by the respiratory muscles.[8] In addition, it is related to mortality and exacerbations, may be an indicator for volume reduction surgery, especially for IC, and the RV/TLC ratio.[9,10]

In principle, a decreased DLco is an indicator of emphysema and may be due to a fall in alveolar volume (AV), mainly due to obstructive defects and/or emphysema, with a fall in the carbon monoxide transfer coefficient (KCO).[11] A DLco value < 60% is associated with decreased exercise capacity, risk of death regardless of the degree of obstruction, and may represent a small group with precapillary pulmonary hypertension.[12] In smokers without obstruction, a value < 80% predicts an increased risk of developing COPD.

The IOS application provides detailed information on airway properties, estimates respiratory system resistance (Rrs) and respiratory system reactance (Xrs). The findings in COPD consist of an increased Rrs and a decreased Xrs value.[13] These findings are suggestive of small airway obstruction and, more importantly, correlate with the severity of obstruction at this level.

The 6MW is a submaximal exercise test. It is a sign of functional capacity in relation to exercise. It can indirectly show maximal oxygen consumption and is considered more representative of patients' daily activity. A reduced distance is an adequate index of functional disability and increased risk of mortality,[14] although the prediction of hospitalization for exacerbation is unclear.

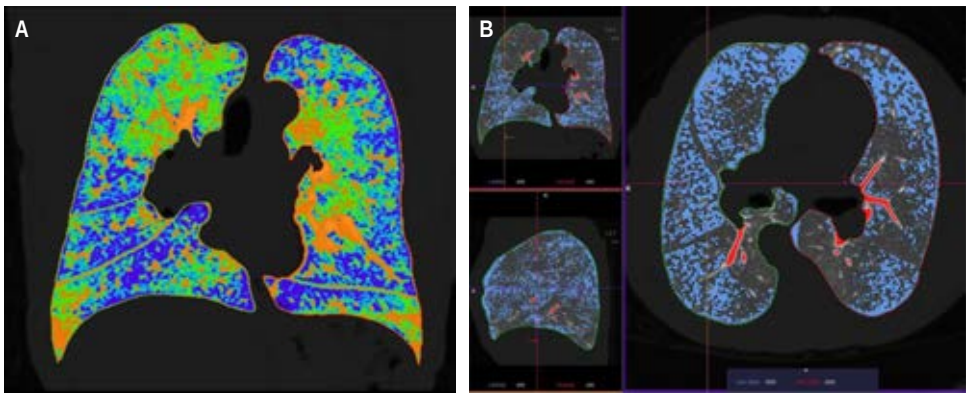

Figure 1:

Representative CT scan of the volumetric evaluation. **A)** The parametric mapping can be seen in coronal plane, where each color corresponds to a voxel with a different percentile, the cut-off point is the 15th percentile. **B)** The evaluation of parametric mapping is observed in multiplanar reconstruction, where all voxels in blue correspond to areas of low attenuation, lower than the cut-off point -950 HU (Hounsfield units).

TOMOGRAPHIC EVALUATION

In 1970 Hounsfield developed computed tomography (CT) for clinical use. Emphysema was described by tomography in the late 1970s and early 1980s. Previously, histologic and postmortem studies were required to evaluate pulmonary structural changes. The introduction of CT made it possible to visualize the thorax and lung structure noninvasively. In 1978, Rosenblum et al. described the areas of low attenuation and average lung density in patients with a clinical diagnosis of COPD.[15]

The need to understand the pathophysiological process of COPD translates into the need to quantify parenchymal and airway damage as a means to closely relate physiological alterations and clinical manifestations. Stereology (spatial interpretation by sections) is the quantification of lung volume by imaging and was initially used in histopathology to be adopted later to quantitative analysis by tomography, to the analysis of normal lung and then expanded to the field of COPD, to provide numerical information of emphysema, and development of a visual stratification system by estimating the number of axial tomography slices, which showed a strong association with airflow obstruction and histological specimens. Subsequently, automated techniques were developed to segment the lung parenchyma and quantify emphysema. The two main techniques initially described used the principle where emphysematous regions are represented by areas of low attenuation: the first method is called tomographic densitometry and the second, percentile densitometry, involves the choice of an average distribution curve, which provides the density in Hounsfield units (HU) under which a percentage of voxels are distributed *(Figure 1)*.[15] The Radiological Society of North America has promoted the standardization of lung densitometry for COPD within the framework of the Quantitative Imaging Biomarkers Alliance® (QIBA®).[16]

Physiopathogenesis and association with imaging

Quantitative histological assessment of the diseased lung, as well as improved lung imaging (such as CT) and a growing understanding of inflammation, cell signaling and cell death, among others, have provided a major step forward in the understanding of COPD. In this context, the determination of lung volumes is a key parameter in pulmonary stereology to properly interpret quantitative damage. Hogg et al. in 1968 provided key physiological data supporting that the main site of increased airway resistance in COPD was the small airways, in the range of 2 mm in diameter,[16] the authors concluded that increased lung resistance could be due to obstruction of the small airways by mucus, narrowing or occlusion by fibrosis, as confirmed by Thurlbeck.[17] The pathogenesis of increased lung volume and pathophysiology of increased small airway resistance includes that related to the cellular inflammatory process and mediated by innate and adaptive immunity. This inflammation persists for several years even after smoking cessation, suggesting self-perpetuating mechanisms.

There is a strong correlation between quantitative assessment of tomographic density and pathologic quantification. The percentage of low attenuation areas by CT are related to the FEV_1/FVC ratio. This shows that smokers with normal spirometry, but with abnormal CT findings, such as emphysema, may have potential to develop airway obstruction in the future, compared to non-smokers.[18] It has been demonstrated with the use of CT for histopathological specimen analysis (microCT) that the number of terminal and transitional bronchioles is reduced by up to 40% in mild to moderate COPD and up to 80% in severe disease. These findings suggest that this airway represents a «silent area» within the lung where damage can accumulate unnoticed.[19] Resistance to small airway airflow is the main site of obstruction in COPD patients and precedes the onset of emphysematous destruction in COPD phenotypes with centrilobulbar

and paraseptal emphysema. Small airways (smaller than 2 mm) cannot be directly visualized using CT scans; therefore, the finding of air trapping, which is seen as decreased lung attenuation on expiratory CT, can be used as an indirect sign of small airway dysfunction in COPD, and can also be quantified volumetrically; this finding is thought to be caused by early collapse of the small airways on exhalation.

Correlation between the extension of emphysema and functional parameters

Visual and subjective assessment of emphysema using CT with contiguous 10 mm thick slices began in 1986; significant correlations were observed between CT visual scores and macroscopic emphysema. Using visual pulmonary assessment, emphysema severity correlates fairly well with physiologic parameters (FEV_1 and FEV_1/FVC) and GOLD stage. The correlation coefficient ranges from 0.67 (for GOLD stage) to -0.74 (for FEV_1/FVC). In particular, the range of the correlation coefficients is similar to the correlations between the extent of emphysema on quantitative CT (QCT) and each physiological parameter (0.62 for GOLD stage and -0.70 for FEV_1/FVC).[16] However, agreement among readers regarding the severity of emphysema on visual assessment tends to be variable, so quantitative CT is preferred for assessing emphysema severity. In addition, CT measurements have been shown to correlate better with macroscopic measurement of emphysema. *Table 1* shows the relationships between tomographic parameters and RFTs.

Regional heterogeneity of emphysema

The basal distribution of emphysema is associated with major alteration of FEV_1, but with less alteration of gas exchange (PaO2) and alveolar-arterial oxygen gradient, compared with the apical distribution of emphysema.[16] Areas of emphysema on CT are more frequently found in the central areas of the lung than in the distal areas, and the extent of central and lower emphysema correlates much more with airflow limitation compared with distal emphysema *(Figure 2)*.

Correlation between airway measurements and functional parameters

Many studies have shown that patients with higher percent wall area (%WA) have lower FEV_1 expressed as a predicted percentage. The %WA has been considered the most commonly employed metric for clinical

Table 1: Application of respiratory function tests in COPD and their relationship with parametric mapping computed tomography.

Test	Clinical outcomes of PFTs	Correlation with CT
Body plethysmography	CI, increased RV/CPT indicate increased dyspnea, risk of death and may be indicative of volume reduction surgery when severe hyperinflation is present	The ITGV and percentage predicted CPT have a positive correlation (R2 0.33) with the percentage of emphysema, with an AUC of 0.79, indicating hyperinflation
Carbon monoxide diffusion	A DLco with values < 60% is associated with decreased exercise capacity and risk of death. Decreased in precapillary pulmonary hypertension. In non-obstructed values < 80% predict a risk of developing COPD	A percentage of predicted decreased KCO and DLco have a positive correlation with the percentage of emphysema especially when greater than 10% with AUC of 0.78
Oscillometry	IOS is more sensitive than spirometry in identifying peripheral airway pathology. In addition, in COPD patients with FEV_1 < 50%, Xrs is a very sensitive indicator of exacerbations and mortality	IOS analysis especially an R5-R20 index > 0.07 kPa has a positive correlation (r2 = 0.599) with small airway disease related to air trapping (OR 2.01) identifying early disease
6 min walk	Reduced distance at 6MW indicates functional disability and increased risk of mortality	The 6-minute walk has a positive correlation with the severity and percentage of emphysema (r = 0.55)
Other spirometry values or indexes	FEV_1/FEV_6 is simple, has good sensitivity, specificity and is a good predictor of exacerbations. FEV_3/FEV_6 values below LLN are associated with poor quality of life, exacerbations and obstruction. Useful for early diagnosis	FEV_1/FEV_6 increased gas trapping and airway wall thickness FEV_3/FEV_6 has a good correlation with small airway disease and emphysema

PFT = pulmonary function tests. AUC = area under the curve. IQ = inspiratory capacity. TLC = total lung capacity. 6MW = 6-minute walk. DLco = diffusing capacity of the lungs for carbon monoxide. COPD = chronic obstructive pulmonary disease. FEV_1 = forced expiratory volume in the first second. FEV_3 = forced expiratory volume at second 3. FEV_6 = forced expiratory volume at second 6. KCO = Korgh's constant. kPa = kilopascals. LLN = lower limit of normal. OR = odds ratio. R5 = total resistances. R20 = central resistances. Xrs = reactance area. ITGV = intrathoracic gas volume. RV = dual volume.

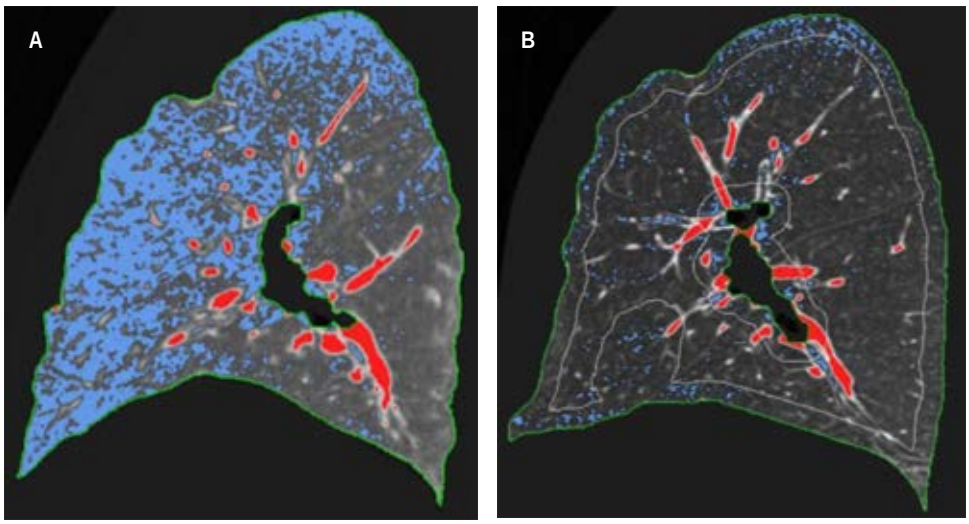

Figure 2:

Sagittal plane parametric mapping. **A)** The predominant distribution of anterior and superior voxels is seen. **B)** Distribution of voxels in blue in the center and periphery of the lung parenchyma; differences in distribution correlate with greater alteration of FEV_1 airflow limitation.

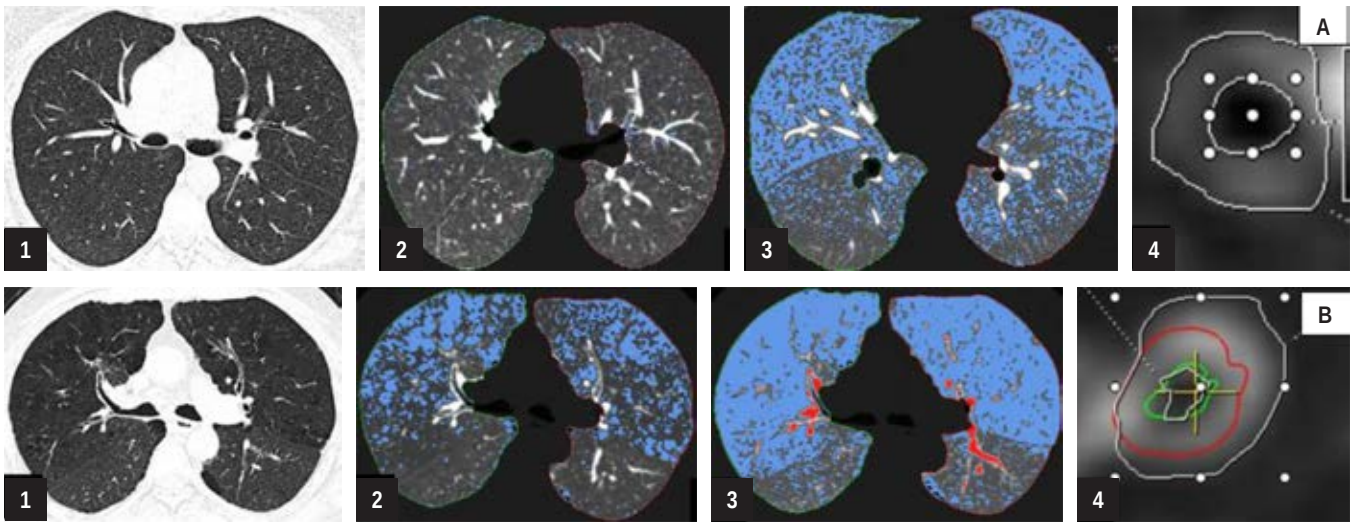

Figure 3: PM CT in patients with COPD and pre COPD secondary to smoking. **A)** CT scan of an ex-smoker patient with dyspnea without spirometric obstruction is shown: CT findings in A1 a normal high resolution CT scan; in A2 the parametric map (PM) shows a volume of 4,482 mL, emphysema index of 3.4%; in A3 PM in expiratory with air trapping of 43.9%, and airway analysis a percentage of wall area (%AP) in A4 of 0.80. His PFTs are characterized by air trapping on body plethysmography (RV/TLC 142% predicted). **B)** Shown is a CT scan of a patient with GOLD 2 COPD due to smoking, dyspnea mMRC2: with centrilobulillar and paraseptal emphysema pattern in B1; PM in B2 with volume of 6,558 mL, emphysema index of 21.9; MPR B3 with air trapping of 56.8% and airway analysis with %AP in B4 of 0.93. His PFRs are characterized by air trapping on plethysmography (RV/TLC 161% predicted, adjusted DLco 57% predicted).

research, and there are modest correlations between it and pulmonary physiologic impairment. Moderate correlations have been described between airway wall measurements and airflow obstruction (FEV_1 and FEV_1 as percent predicted) and stronger correlations are observed when only small airways are analyzed. Relative volume change (RVC) is the parameter that shows that air trapping can be quantified based on the relative lung density in expiration and inspiration, thus expressing the actual degree of air trapping as the difference of the relative percentage of the thresholds in inspiration (-950 HU) and expiration (-860 HU).

Other methods are the air trapping index, which includes the ratio of expiratory to inspiratory lung volume (E/I-LV ratio) and the expiratory to inspiratory ratio of mean lung density (E/I-MLD ratio). E/I-MLD correlates with COPD clinical parameters such as BODE index (r 0.48 - 0.68) and E/I-LV shows a very high correlation with E/I-MLD ($r = 0.95$, $p < 0.001$).[16]

Other evidence has found small airway dysfunction, related to the degree of trapping and the percentage of damage on the parametric map *(Figures 3 and 4)*; small airway dysfunction as assessed by IOS parameters in COPD patients is present in all exacerbations of the disease, particularly in GOLD patients 3-4. Compared to patients with normal IOS parameters, patients with abnormalities in IOS parameters have more respiratory symptoms, more severe airway obstruction, and structural abnormalities on imaging.[15]

OTHER IMAGING METHODS

Magnetic resonance (MR) imaging can provide functional information using perfusion and ventilation techniques in patients with COPD; with the MR perfusion technique, pulmonary blood flow can be quantitatively assessed. Perfusion alterations in COPD often show a low degree of inhomogeneous contrast enhancement, especially in areas of severe emphysema and with decreased peak signal intensity. In patients with severe emphysema, visual assessment of perfusion by 3D MRI shows high concordance with parenchymal destruction. Quantitative analysis confirms decreased perfusion parameters and correlates with worsening FEV_1/FVC and increased CT emphysema index. Perfusion MRI in COPD shows reduced value and heterogeneous change in mean pulmonary blood flow (MBF), pulmonary blood volume (PBV) and mean transit time (MTT) compared to normal volunteers. Other advances in magnetic resonance imaging are those assessed by hyperpolarized gases, such as helium and xenon, which are expressed by ventilatory defects and can be quantified through the apparent diffusion coefficient (ADC) expressed in percentages; these ADC ventilatory defects correlate significantly with lung function tests (FEV_1, FEV_1/FVC and DLco).[16]

Dual-energy computed tomography, another imaging technique for the evaluation of COPD patients, shows that anatomical changes influence alveolar gas exchange and pulmonary blood flow. Pulmonary blood volume, assessed by this technique can be used for pulmonary perfusion assessment as a surrogate for dynamic CT-derived pulmonary blood flow; a simpler protocol that maintains quantitative similarity.

Dynamic perfusion imaging with multidetector CT can also provide regional perfusion. Smokers with subtle findings of centrolobulillar emphysema on CT and normal spirometry have been shown to have increased regional heterogeneity of lung perfusion compared with never-

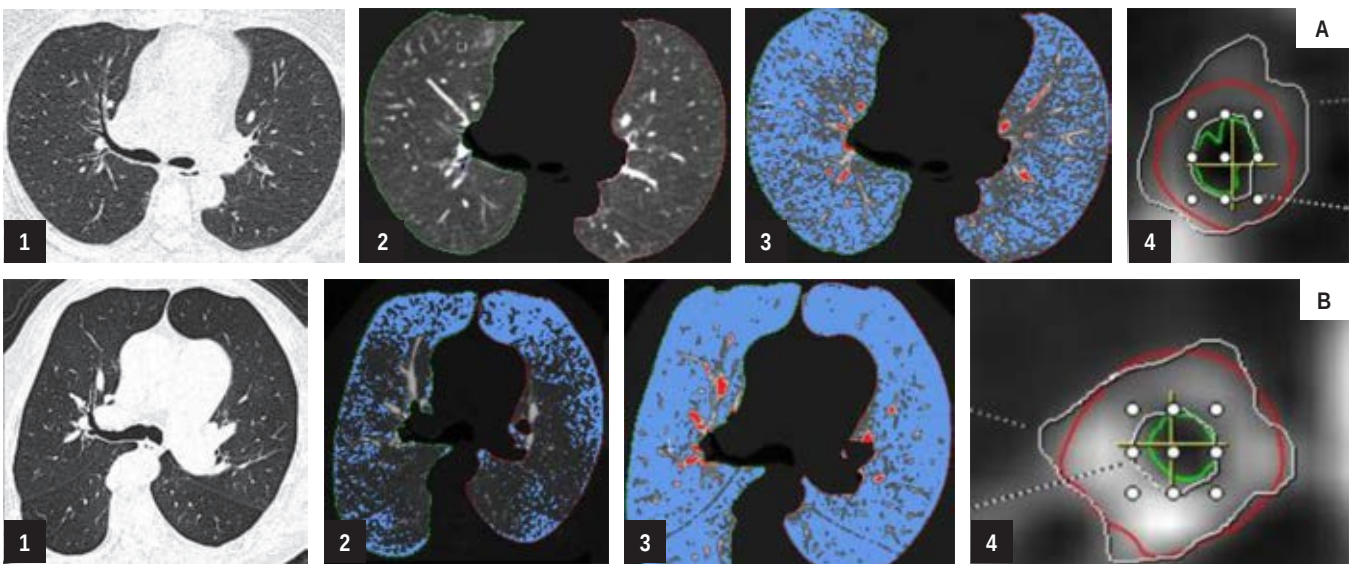

Figure 4: Parametric computed tomography map in patients with wood smoke damage at different stages of the disease. **A)** A CT scan of a patient exposed to wood smoke, chronic bronchitis without spirometric obstruction is shown: with normal high-resolution CT in A1; in A2 PM with volume of 3,960 mL and practically null emphysema index of 0.9%; in A3 MPR expiratory with air trapping of 40.9%, and %AP in A4 of 0.81. His PFTs are characterized by increased small airway resistances on oscillometry (R5Hz 146% pred, R20Hz 130% pred, R5Hz-R20Hz 0.15 KPa L/s). **B)** A CT scan of a COPD GOLD 2 patient exposed to wood smoke, chronic bronchitis is shown: the CT scan demonstrates in B1 mosaic pattern, low attenuation centrilobulillar nodules and an increase in the anteroposterior axis of the rib cage; in B2 PM with volume of 3,973 and emphysema index of 25%; B3 PM significant expiratory air trapping of 75.8% and in B4 %AP of 0.84. Their PFTs are characterized by increased small airway resistances in oscillometry (R5Hz 265% pred, R20Hz 142% pred, R5Hz-R20Hz 0.6 KPa L/s).

smokers and smokers with normal CT imaging. This technique requires a central bolus of high-pressure contrast material and scans a limited axial extent of the lung during a synchronized cardiac scan.

Xenon is a radiopaque gas and its concentration in the alveolar space can be measured as a function of CT image attenuation changes. Due to variability in baseline lung attenuation, between images due to misregistration artifacts and different levels of respiration, accurate measurement of lung ventilation function is limited. Two stable gases, xenon and krypton, with high atomic numbers (54 and 36, respectively) are eligible for dual-energy CT ventilation imaging. For xenon ventilation imaging with dual-energy CT, the patient generally inhales stable xenon at a concentration of 30% (mixture of 30% xenon and 70% oxygen) for 1 min to 1 min and 30 seconds and with the use of a xenon gas inhalation system.

Regional ventilation and perfusion can also be assessed with positron emission tomography (PET), using 13N2 isotope as a gas dissolved in saline. Spatial heterogeneity of lung perfusion has also been described with 13N2-saline PET, and regional heterogeneity in perfusion has been increased in patients with mild COPD compared with healthy controls, after adjusting for regional changes in lung tissue density and ventilation. These results suggest that regional perfusion changes may precede lung parenchymal destruction in COPD. Therefore, this imaging method may serve as an early biomarker.

CONCLUSIONS

There is an adequate correlation of PFT and quantitative assessment by CT, as well as other imaging techniques. This has allowed to broaden the knowledge of the pathophysiological process; its multiple metrics show usefulness for the detection of initial findings in early COPD. Furthermore, CT imaging with parametric mapping is emerging to improve the diagnosis and allow the follow-up of this type of patients, as well as for the implementation of early therapeutic strategies.

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Conflict of interests: the authors declare that they have no conflict of interests.

NCT
Neumología y Cirugía de Tórax
Vol. 82 - No. 1 / January-March 2023

Review
doi: 10.35366/114226

Importance of the bactericidal antimicrobial protein that increases permeability in respiratory diseases

Importancia de la proteína antimicrobiana bactericida que aumenta la permeabilidad en enfermedades respiratorias

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ABSTRACT. The bactericidal permeability increasing protein is a molecule of the immune system which participates in the defense against pathogens. This protein binds to Gram-negative bacterial membranes altering permeability and inducing lysis. It also binds to free lipopolysaccharides, inhibiting Theo sígnala chat leads no inflamarían. In admitían, tris porten induces he opsonization activity contributing to phagocytosis. The role of the bactericidal permeability increasing protein, during infections by Gram-positive bacteria is still controversial. However, this protein increases in meningitis caused by *Streptococcus pneumoniae* and *Neisseria meningitidis* and during respiratory infections caused by the influenza A virus, possibly modulating the production of proinflammatory cytokines. In other respiratory disorders such as chronic obstructive pulmonary disease, cystic fibrosis, and asthma, the production of autoantibodies against this protein is recurrent. This antibody production reduces the bactericidal permeability increasing protein serum levels, decreasing antimicrobial defense against pulmonary infections. Therefore, it is essential to understand the role of this protein during respiratory diseases to propose possible therapies to improve patient health.

Keywords: bactericidal protein that increases bacterial permeability, microbial infections, inflammation and autoimmunity.

RESUMEN. La proteína bactericida que aumenta la permeabilidad es una proteína del sistema inmune que participa en la defensa contra patógenos. Esta proteína puede unirse a las membranas de bacterias Gram negativas, alterando la permeabilidad e induciendo la lisis. También se une a los lipopolisacáridos libres al inhibir la señalización que lleva a la inflamación. Además, esta proteína induce opsonización, contribuyendo a la fagocitosis. El papel de la proteína bactericida que aumenta la permeabilidad, durante las infecciones por bacterias Gram positivas aún es controversial, pero se ha demostrado su inducción durante la meningitis ocasionada por *Streptococcus pneumoniae* y *Neisseria meningitidis* y durante infecciones respiratorias generadas por el virus de la influenza A, posiblemente modula la producción de citocinas proinflamatorias. En otros padecimientos respiratorios como: la enfermedad pulmonar obstructiva crónica, la fibrosis quística y el asma, se producen por lo común autoanticuerpos contra esta proteína, disminuyendo sus niveles séricos, lo que repercute en la defensa contra infecciones pulmonares. Por ello, es importante comprender el papel de la proteína bactericida que aumenta la permeabilidad durante las enfermedades respiratorias, con el fin de proponer posibles terapias para mejorar la salud de los pacientes.

Palabras clave: proteína bactericida que incrementa la permeabilidad bacteriana, infecciones microbianas, inflamación y autoinmunidad.

Abbreviations:

BPI = bactericidal/permeability increasing protein.
COPD = chronic obstructive pulmonary disease.
RNS = reactive nitrogen species.
ROS = reactive oxygen species.
FEV_1 = forced expiratory volume in 1 second.
CF = cystic fibrosis.
FVC = forced vital capacity.
LBP = lipopolysaccharide-binding protein.
LPS = lipopolysaccharide.
TNF-α = tumor necrosis factor alpha.

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Received: VII-05-2023; accepted: IX-11-2023.

How to cite: Guzmán-Beltrán S, Luna-Villagómez HA, Páez-Cisneros CA, Santos-Méndez MA, Reyes-Lazcano ME. Importance of the bactericidal antimicrobial protein that increases permeability in respiratory diseases. Neumol Cir Torax. 2023; 82 (1): 29-35. https://dx.doi.org/10.35366/114226

INTRODUCTION

The purpose of the immune system is to protect organisms from infectious agents.[1,2] Macrophages and neutrophils are cells of the immune system with the ability to ingest pathogens, effectively destroying them in phagosomes by generating reactive oxygen and nitrogen species (ROS and RNO) and protein-based antimicrobial molecules, contributing to a multifaceted, coordinated and highly effective defense. ROS produced by neutrophils and macrophages are: superoxide anion (O_2-), hydrogen peroxide (H_2O_2) and hypochlorous acid (HOCl); while RNS are: nitric oxide (NO), nitrogen dioxide (NO_2) and peroxynitrite (ONOO-).[1] These species are highly toxic to pathogens, leading to their death.

However, some pathogens, such as *Candida albicans* and *Staphylococcus aureus*, are resistant to oxidative attack; therefore, the production of antimicrobial peptides and proteins is necessary to eliminate the pathogen.[3,4] Antimicrobial peptides include defensins, granzymes, cathelicidins, and other cationic peptides and proteins such as lactoferrin and bactericidal/permeability increasing protein (BPI) to ensure the elimination of pathogens.[2,5]

The aim of this review is to show the importance of BPI during various respiratory diseases. The mechanisms by which BPI contributes to pathogen clearance will be explored and a comprehensive view of the importance of BPI as an essential component of the immune response will be provided.

GENERAL CHARACTERISTICS OF BPI

The BPI protein is a member of the family of lipid transporter proteins, which can bind to various lipid molecules such as lipopolysaccharides (LPS). The different members of the family include proteins involved in the innate immune response, such as: LPB (Lipopolysaccharide-Binding Protein), PLUNC (Palate, Lung, and Nasal epithelium Clone), CETP (Cholesteryl Ester Transfer Protein) and PLTP (Phospholipid Transfer Protein).[6]

BPI is expressed in various cell types such as: neutrophils, polymorphonuclear cells, eosinophils, macrophages, platelets and epithelial cells.[7] BPI is composed by 456 amino acid residues, with a molecular weight of 55,000 Daltons (Da), of cationic nature.[8] In X-ray crystallography analysis, BPI has a bipartite boomerang-shaped structure composed of two main domains: an amino-terminal domain (N-terminal) and a carboxy-terminal domain (C-terminal), separated by a proline-rich region. It has two apolar lipid binding sites, one in each half of the molecule, allowing it to bind to the hydrophobic acyl chains of LPS.[9]

The primary structure of BPI reveals that the N-terminal region is positively charged due to the abundance of basic residues, mainly lysine. The cationic characteristic of antimicrobial proteins and peptides allows them to interact with LPS found in the negatively charged bacterial envelope.[10] BPI is an essential molecule in the immune response, as it has antimicrobial action, opsonizing effect and anti-inflammatory activity.[7] The three-dimensional structure of the protein is illustrated in *Figure 1*.

IMPORTANCE OF BPI IN RESPIRATORY DISEASES

Respiratory diseases represent a major global problem. Infectious diseases cause millions of deaths worldwide, for example, influenza A virus infections occur worldwide and cause between 3 and 5 million severe cases and between 0.29 and 0.65 million deaths. Each year, tuberculosis kills 1.6 million people, while 2.5 million die of pneumonia, 30% of whom are children under five years of age. Other non-infectious respiratory diseases that cause human losses are: chronic obstructive pulmonary disease (COPD), which is the third leading cause of death worldwide, causing 3.23 million deaths in 2019 alone. Asthma causes an average of 1,000 deaths per day;[11] as for cystic fibrosis (CF), despite being a rare disease, an average of 300 people are born with this condition in Mexico.[12]

In several respiratory diseases, it has been described that the BPI protein presents high levels, playing an essential role in several diseases. This can be explained because it has the capacity to fight infections, regulate inflammation and modulate the immune response in the lungs, which makes it a key factor in the protection of the respiratory system. It is possible that BPI has potential as a diagnostic marker or even has therapeutic use in treating infections. In fact, BPI has been shown to play a crucial role in the prevention and treatment of respiratory diseases such as viral and bacterial infections, as well as COPD, CF and asthma.

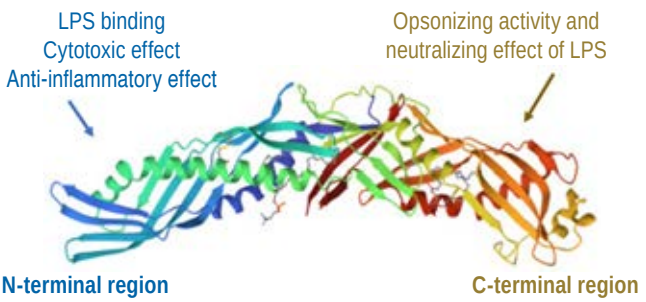

Figure 1: Structural and functional characteristics of BPI. The N-terminal region binds to lipopolysaccharide (LPS) of living bacteria forming pores on the cell surface. In addition, it has anti-inflammatory effect while the C-terminal region enhances opsonization.
Illustration modified from: Beamer LJ, *et al.*[9]

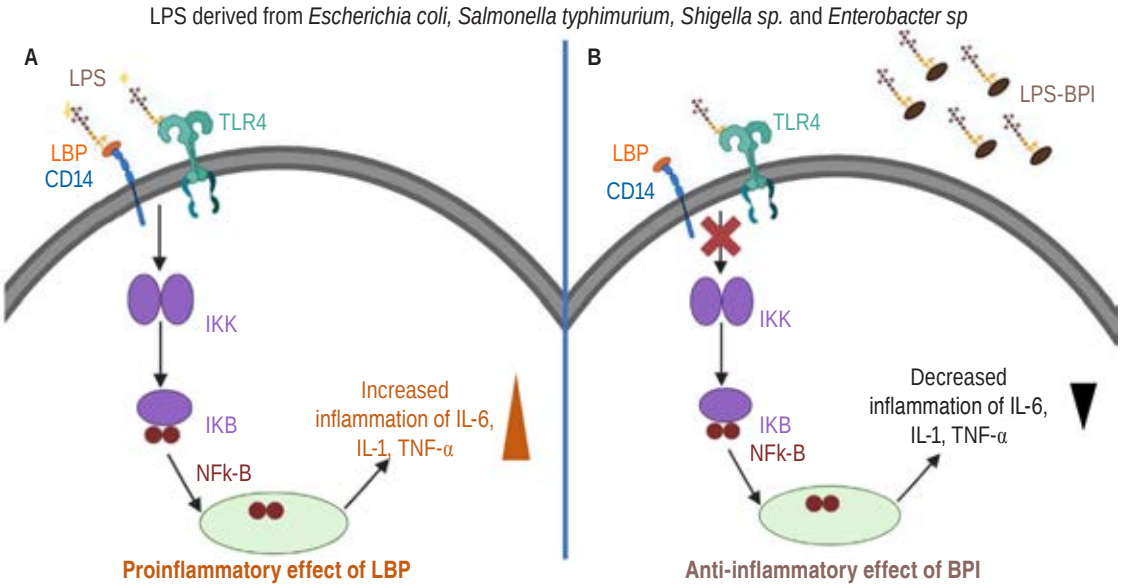

Figure 2: Mode of action of LBP and BPI. LPS bound to LBP is able to activate an inflammatory state by binding to CD14 and TLR4 **(A)**. Whereas BPI can bind free LPS and prevent LBP signaling by decreasing the production of proinflammatory cytokines **(B)**.
LBP = lipopolysaccharide-binding protein. LPS = lipopolysaccharide. BPI = bactericidal/permeability increasing protein. IKK = protein kinase. IKB = inhibitor of NF-kappa-B. NFk-B = nuclear factor kappa B. TLR4 = toll-like receptor 4. CD14 = cluster of differentiation. IL-1 and IL-6 = interleukins 1 and 6. TNF-α = tumor necrosis factor alpha. Figure created with BioRender.com

BPI in bacterial infections

The ability of BPI to bind to LPS allows it to have antibacterial action towards Gram-negatives such as *Escherichia coli*, *Salmonella typhimurium*, *Shigella* and *Enterobacter* spp, being effective at nanomolar concentrations.[2,10]

The selective binding of BPI to lipid A of LPS and to bacterial surface phospholipids of living bacteria causes increased membrane permeability and formation of pores in the wall, allowing entry of other antimicrobial molecules and generating loss of proton motive force, lysing the bacteria. The positive charge of the amino-terminal domain of BPI interacts with the negative charge of LPS.[13]

BPI has an anti-inflammatory effect by preventing the production of proinflammatory cytokines triggered by LPS. BPI belongs to the above-mentioned family of lipid transfer proteins, which also includes lipopolysaccharide-binding protein (LBP), which is present in serum.[14,15] Unlike LBP, which facilitates proinflammatory activation of monocytes by LPS, binding of BPI to LPS reduces its ability to trigger endotoxin activation.[16] LBP catalyzes and disperses LPS aggregates and binds LPS monomers to CD14/TLR-4 receptor complexes, triggering the release of proinflammatory cytokines.[16] Due to its high affinity for LPS, BPI increases the size of LPS aggregates, which prevents LPS from interacting with LBP and reduces the production of proinflammatory cytokines by macrophages.[16-19] *Figure 2* illustrates the anti-inflammatory mode of action of BPI and the opposite effect of LBP protein.

Likewise, the opsonizing effect of BPI has been described, which is attributed to the carboxyl domain of the protein, since it enhances the delivery of vesicles derived from the outer membrane of Gram-negative bacteria to dendritic cells. Preincubation of *E. coli* with 50 nM BPI was shown to increase phagocytosis in neutrophils in the absence of serum, but increases to 100% in the presence of serum, which accelerates opsonization by complement proteins.[20]

In a model of lung infection caused by *Pseudomonas aeruginosa*, *Streptococcus pneumoniae* or *Streptococcus agalactiae*, it was shown that a recombinant BPI_{21} fraction (21 amino acids of the N-terminal region) improved the survival of mice infected with these strains by inducing apoptosis of infected cells. In addition, bronchial lavage cells from infected mice were shown to exhibit high expression of BPI.[21]

On the other hand, in patients with meningitis caused by *S. pneumoniae* and *Neisseria meningitidis*, there is significant increase of BPI in cerebrospinal fluid.[22] Furthermore, they demonstrated that BPI can bind specifically to teichoic acids and lipopeptides, suggesting that BPI is a molecular pattern recognition molecule associated with bacteria in general. Furthermore, interaction of BPI with molecules derived from Gram-positive bacteria induces the expression of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6).[22]

It was also shown in a model of human macrophage infection with *Mycobacterium tuberculosis* that treatment with inflammation-resolving lipids such as maresin 1 and resolvin D induced BPI expression and significantly decreased intracellular growth of mycobacteria, suggesting an important role in infections caused by Gram-positive bacteria.[23]

BPI in viral infections

Influenza is a common infectious disease, the most frequent causative agent being the influenza A virus, which is a very successful pathogen, circulating constantly in diverse hosts such as humans, pigs, horses, dogs and birds.[24] Annual epidemics of seasonal influenza result in millions of infected people worldwide.[25]

In an in vitro model, influenza A virus variants (H1N1, H3N2 and H5N1) were found to induce the release of BPI from human granulocytes.[26] It was found that a recombinant BPI_{27} fraction (27 amino acids of the N-terminal region) is able to inhibit viral infectivity and modify the structure of the influenza A H1N1 virus in human mononuclear cells.

In the same model, they also showed that cells infected with influenza A H1N1 virus treated with the BPI27 fraction significantly decreased interferon alpha (IFN-α) and IL-6 production in a concentration-dependent manner.[26]

Although there is high basal expression of BPI in diverse cell types such as gastrointestinal epithelial cells, dermal fibroblasts, basal epithelial cells of the ducts of the excretory lacrimal glands and of the genital tract in humans, the role of BPI in various infections and its contribution to the elimination of viral pathogens is unknown.[27-30]

BPI in patients with chronic obstructive pulmonary disease (COPD).

COPD is characterized by persistent respiratory symptoms such as dyspnea, chronic cough and mucoid sputum production, decreased airflow due to airway or alveolar abnormalities. As for its pathophysiology, there is an increase in the number of goblet cells, hyperplasia of the mucous glands, collapse of the airways due to destruction of the alveolar wall, narrowing and decrease in the number of small airways, fibrosis of the lung parenchyma and recurrent infections.[31]

The main pathogen associated with COPD is *P. aeruginosa*, which contributes to the production of autoantibodies against BPI (anti-BPI), decreasing the ability to clear the bacteria and inducing an exacerbated inflammatory response.[32] It was shown that anti-BPIs are formed from a pathway dependent on CD18, a β-2 integrin, necessary for phagocytosis that acts if BPI and microbial antigen are taken up simultaneously and together are presented to major histocompatibility complex (MHC) class II molecules on the cell surface to generate the production of autoreactive antibodies against BPI.[33] Anti-BPI production in COPD patients causes increased neutrophil recruitment and increased production of inflammatory cytokines such as TNF-α, interleukin-1 beta (IL-1β) and IL-6, decreasing the antimicrobial and anti-inflammatory effect. In addition, patients who produce anti-BPI present pulmonary dysfunction, manifesting a decrease in the total exhaled fraction in the first second (FEV1) and total exhaled volume fraction (FVC).[32]

In another study, a group of volunteers (all men) with COPD exhibited decreased plasma BPI concentration compared to the control group (10.6 ± 2.2 versus 23.4 ± 2.1 ng/mL, $p < 0.0001$). Indeed, there was an association of low BPI levels with patient severity. Lower BPI leads to increased circulating LPS by increasing TNF-α levels, which generates greater inflammation and, therefore, greater clinical manifestations in COPD patients.[34]

BPI in patients with cystic fibrosis (CF)

During CF or mucoviscidosis, thick, viscous mucus is produced, causing obstruction of the ducts of the organs where it is located, with the pancreas and lungs being the most compromised organs. The accumulation of thick mucus leads to blockage in the airways, as well as repeated episodes of inflammation, lung damage and recurrent respiratory infections that affect the quality of life of thousands of people worldwide.[35]

CF is caused by mutations in the gene that produces the CF transmembrane conductance regulator (CFTR) protein. This protein is responsible for regulating the flow of salt and fluids in and out of cells in different parts of the body. In CF, the CFTR protein may be absent or dysfunctional, resulting in decreased water movement, which causes more thick mucus to accumulate.[36]

CF patients have recurrent infections with *S. aureus, Streptococcus pneumoniae, Burkholderia cepacia, Haemophilus influenzae, Achromobacter xylosoxidans, Stenotrophomonas maltophilia, P. aeruginosa* and some mycobacteria.[37] Seventy percent of patients may be co-infected by different pathogens. For example, *S. aureus* and *P. aeruginosa* can persist together with *H. influenzae* or *S. pneumoniae*; however, the microorganism that most frequently colonizes the respiratory tract in patients with CF is *P. aeruginosa*, which generates chronic pulmonary deterioration.[38]

It has been shown that in CF patients during infection with *P. aeruginosa*, antibodies to the bacterium and to the BPI protein are also induced.[35] These anti-BPI autoantibodies have a variable prevalence in at least 50% of people with CF. Therefore, anti-BPIs are considered a useful

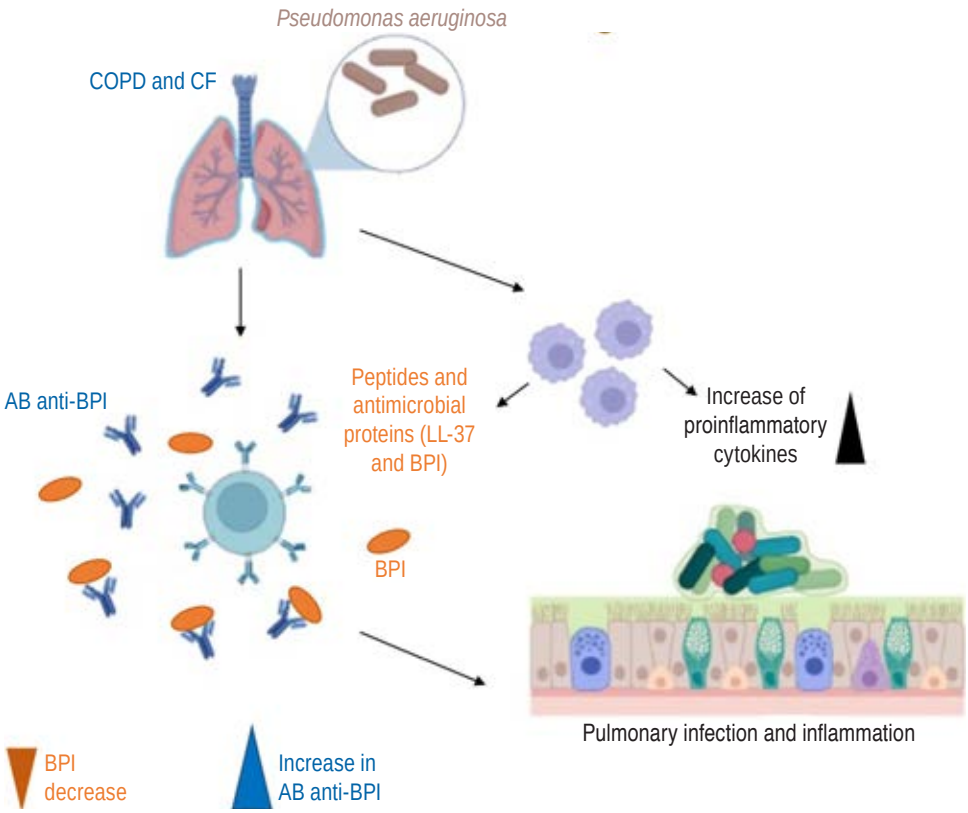

Figure 3:

Effect of anti-BPI antibodies on inflammation. During *P. aeruginosa* infection in patients with CF and COPD, anti-BPI antibodies are produced that decrease serum BPI levels, cause exacerbated inflammation and rapid progression of the infection. BPI = bactericidal/permeability increasing protein. CF = cystic fibrosis. COPD = chronic obstructive pulmonary disease. Figure created with BioRender.com

prognostic marker, as patients with high serum levels have increased lung damage leading to lung transplantation or premature death.[39,40] *Figure 3* illustrates how autoantibodies are generated and their involvement during an infection and their impact on the overall inflammatory state.

BPI in patients with asthma

Asthma is a heterogeneous and multifactorial disorder, characterized by reversible symptoms and it appears in episodes. However, as the disease progresses, permanent airway changes appear, such as smooth muscle hypertrophy and hyperplasia, as well as hypersecretion of the mucous glands.[41,42]

It has been shown that people with asthma have high levels of BPI. The serum BPI concentration of patients with uncontrolled asthma was three times higher (18.10 ± 13.48 ng/mL) compared to healthy controls (6 ± 2.27 ng/mL). Even patients with controlled asthma showed increased serum BPI (12.83 ± 6.04 ng/mL) compared to control. Then, when comparing serum BPI concentration with clinical indicators of patients with asthma, no significant relationship was found between BPI, eosinophil levels, IgE antibodies, fractional exhaled nitric oxide (FeNO) and percentage of FEV1. However, there is a significant positive correlation between BPI concentration and C-reactive protein, suggesting BPI as a possible biomarker for asthma.[43]

CONCLUSION

It has been demonstrated that BPI has a direct antimicrobial effect, neutralizes endotoxins and prevents the generation of antibiotic resistant strains due to its protein nature. In addition, BPI has no toxic effects, induces opsonization and has an anti-inflammatory effect; therefore, it is possible that BPI generates synergy with conventional antibiotics and antivirals. BPI has proven to be a promising therapeutic molecule that can control infection and inflammation in different diseases. A viable alternative could be to use recombinant BPI and induce the expression of endogenous BPI in the host, in order to contribute to the elimination of pathogens even in diseases where anti-BPI antibodies are generated.

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Conflict of interests: the authors declare that they have no conflict of interests.

NCT
Neumología y Cirugía de Tórax
Vol. 82 - No. 1 / January-March 2023

Ideas and perspectives

doi: 10.35366/114227

Respiratory Medicine of systems

Medicina respiratoria de sistemas

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In the late 1980s, I heard professors say: «90% of diagnoses are made with medical records». The challenge was, then, to integrate information. The information obtained in the medical record made sense after connecting the symptoms and signs, and the nosological diagnosis was establish. Currently, more than 30 years later, 90% of the diagnoses are established with additional studies, mainly imaging and often molecular. Technology has largely replaced clinical thought. That good medical record stopped being important and the Computer Tomography (CT) or the whole-body Positron Emission Tomography was introduced. There is no doubt that medicine has evolved, technology has allowed to practice more scientific medicine and less artistic; more precise, predictive, and even, personalized. Currently, in medicine as in science, we live the better times, but with an increasingly wide gap between what should be done and what is done in the social scope of medicine.

Medical practice has been based, for centuries, on the reductionist approach of science. Since Descartes, in the first half of the seventeenth century, science has been concerned with learning more about the components of the system. That is to say, that the individual elements have been the protagonists in the long and difficult path of reductionism. Although it was successful, reductionism felt short in the understanding of the biological systems. The Human Genome Project, probably far-reaching plan in the reductionist era of science, has failed to fully understand the functioning of the human body; and, yet again, the individual elements, even individual molecules do not explain the whole. Epigenetic is a good example of the importance of interactions. The medicine of systems is based on the interactions between its components, and not on the individual components. The system has emergent properties that derived from precisely the bidirectional, complex and simultaneous interaction between its elements. In axiomatic words; the system (the whole) is much more than the sum of its parts.

The opposite of reductionism is the approach that integrates; joins, interacts, connects. We are returning to see the macro, from a distance, through the integrative approach of science. The development of science has been a continuum. In other words, the path of reductionism has been necessary to understand that the molecular knowledge is not enough to understand the whole. The connectome is the map of connexions, of interactions.

Our brain works based on «reference frameworks». According to Jeff Hawkins,[1] those reference frameworks are used by our brains, by thousands or by hundreds of thousands, to construct the reality of our world. What we perceive as reality is a brain construct based on reference frameworks. In a simpler form, medicine is also based on reference frameworks or patterns. We recognize patterns to identify diseases. But, again, patterns or diseases are half-truth. In that recognition of patterns more and more subpatterns have been identified and we have created the phenotypes, endotypes, etiotypes of diseases. Supporting the concept of «patterns» might not be the best solution. We might have to understand and implement the model

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Received: VIII-20-2023; accepted: IX-14-2023.

How to cite: Torre-Bouscoulet L. Respiratory Medicine of systems. Neumol Cir Torax. 2023; 82 (1): 36-37. https://dx.doi.org/10.35366/114227

of interactions and make way for the medicine of systems where each variable (genetic or epigenetic) will have a specific and dynamic contribution in the pathophysiological process. How truth in that phrase: «there are sick people (systems), not diseases (patterns)». Let's leave behind the model in which a pattern was made fit to a subject; better let's analyze the way in which the variables (the elements) interact to create the biological reality of an individual.

Artificial Intelligence (AI), a technological process that aims to simulate human intelligence, has contributed in a significantly to the understanding of the biology of the systems. Nonetheless, AI requires being feed with information; in other words, the computer needs -to learn- to create predictive models. In its progressive and inexorable path towards improve its predictive ability, AI will be -or is it?- the primary provider of health services and eventually, it might replace clinical human reasoning with its almost infinite algorithms to generate diagnoses and to establish treatments and prognoses. Even more, robots with their intelligence -even if it is artificial- it will be the surgeons the ones who will flood the operating rooms around the world and, thus, the human reasoning could be less and less necessary. I do not doubt that human reasoning will be replaced by the, hopefully sufficiently intelligent, reasoning of machines. It is very likely that if we attend to the conclusions of AI, we will obtain better results for the common and individual good than those we would obtain from human reasoning. What I am not sure about whether the machines can deal with the absence of information; I mean, the models derived from AI work with what exists, with data, with evidence, with information; but, what if in the clinical exercise we must deal with what does not exist? For example, with the uncertainty? In AI, the total is equal to the sum of its parts; in natural intelligence, the total is not equal to the sum of its parts.

The artistic part of medicine is reduced today, I believe, to the management that we give with to the non-existent, to uncertainty. It is possible that human intelligence outweighs the artificial intelligence when there is no data that can provide certainty. AI works with data, not with an absence of data. On a smaller scale, this can be illustrated by the multivariate models that we frequently find in scientific publications. Let's say you build a mathematical model from certain variables to predict lung function. This model, when it takes into account the sex, height and age, will give us inevitably a prediction that will have a certain degree of imprecision, of error. The better the determinants of respiratory function are known, the grater the accuracy of the model. At the time, thanks to the contributions of Newton and others, the laws of classical mechanics were known and astronomical phenomena were predicted in seconds. On the contrary, if all the determinant factors of climate are not fully known, the models cannot be fed to generate sufficient accuracy in their predictions. That is, the prediction fails if there are gaps in the models. Clinical practice is full of gaps; of things that are missing. In terms of the symptoms, which are the most frequent reason why people go to the doctor, are, ultimately, sensations that each subject experiences differently. The symptoms derive from the effect of a stimulus on our consciousness; How many gaps can there be in this process so subjective as to be able to take it to a mathematical model for predictive purposes? How is the connection map (connectome) when aspects such as dyspnea, cough, precordial oppression, or even more subjective such as fear, anxiety, depression, quality of life, insomnia are included in the covariates?

I know little about the theories of education, but I witness that the medical student and residents are bombarded with diagnostic and therapeutic processes based on algorithms as if the implementing of algorithms were what makes the doctor. In the creation and implementation of algorithms, AI has a wide advantage. We cannot, nor should we train medical «algorithmologists»; they are going to be overtaken very soon (or they are being overtaken) by AI. For the doctors who pride to be one, AI will be a tool that allows them to make their work more efficient; for the rest, AI will be their substitute.

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Conflict of interests: the author declares that he has no conflict of interests.

NCT
Neumología y Cirugía de Tórax
Vol. 82 - No. 1 / January-March 2023

Clinical case

doi: 10.35366/114228

Primary ciliary dyskinesia. Cause of recurrent respiratory infections: series of three cases

Discinesia ciliar primaria. Causa de infecciones respiratorias recurrentes: serie de tres casos

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ABSTRACT. Primary ciliary dyskinesia is a rare autosomal recessive genetic disease affecting ciliary movement. The clinical manifestations of the disease can present from birth with respiratory distress syndrome or during childhood with chronic productive cough and non-seasonal rhinosinusitis, recurrent respiratory infections that even require in-hospital management, so it should be considered as part of the approach to study recurrent infections in the pediatric patient. **Clinical cases:** we investigated the evolution and relevant history of three patients entitled to the Secretary of the Navy with recent diagnosis of primary ciliary dyskinesia by electron microscopy and genetic panel who presented recurrent infections in childhood, which required in-hospital management on several occasions. The aim of this article is to keep in mind the disease as a cause of recurrent respiratory tract infections in order to perform an adequate approach, avoiding sequelae in our patients secondary to a late diagnosis.

Keywords: ciliary dyskinesia, respiratory infections, chronic cough.

RESUMEN. La discinesia ciliar primaria es una enfermedad genética poco frecuente, autosómica recesiva, que afecta el movimiento ciliar. Las manifestaciones clínicas de la enfermedad pueden presentarse desde el nacimiento con un síndrome de dificultad respiratoria o durante la infancia con tos crónica productiva y rinosinusitis no estacional, infecciones respiratorias recurrentes que incluso requieran manejo intrahospitalario, por lo que se deberá considerar como parte del abordaje de estudio de infecciones recurrentes en el paciente pediátrico. **Casos clínicos:** se investigó la evolución y antecedentes de importancia de tres pacientes derechohabientes de la Secretaría de Marina con reciente diagnóstico de discinesia ciliar primaria por microscopia electrónica y panel genético; presentaron cuadros de infecciones recurrentes en la infancia, los cuales requirieron manejo intrahospitalario en varias ocasiones. El objetivo del presente artículo es tener presente la enfermedad como una causa de infecciones recurrentes de vías respiratorias para realizar un adecuado abordaje, evitando secuelas en nuestros pacientes secundario a un diagnóstico tardío.

Palabras clave: discinesia ciliar, infecciones respiratorias, tos crónica.

INTRODUCTION

Primary ciliary dyskinesia (PCD) is a rare genetic disease, usually presenting with an autosomal recessive inheritance pattern affecting cilia movement, mainly affecting the DNAH5 and DNAI1 genes.[1] It is considered an early-onset disease with no gender, ethnic and/or racial predilection, with a frequency of 1 in 10,000-20,000 live newborns, with an increased prevalence of up to 5% in patients with recurrent respiratory tract infections in European countries.[2]

Cilia are organelles found on the cell surface. There are two types of cilia: immotile and motile; each cilium is composed of a cytoskeleton, called axoneme, composed of nine longitudinal microtubule doublets that surround a central pair, forming the 9 + 2. Each peripheral microtubule doublet has an outer arm and an inner arm of dynein, which contains the motile protein of the cilium.[3] Seventy percent

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Received: I-28-2023; Accepted: VIII-07-2023.

How to cite: Leal-Jiménez E, Avilés-Ramírez BA, Reyes-Rosales M. Primary ciliary dyskinesia. Cause of recurrent respiratory infections: series of three cases. Neumol Cir Torax. 2023; 82 (1): 38-41. https://dx.doi.org/10.35366/114228

of patients with PCD have a pathogenic variant in a gene related to cilia function, causing structural and functional changes. In the case of PCD, the condition is found in motile cilia responsible for the sweeping action, mobilizing fluids and debris unilaterally. When a defect in this movement is found, the patient will present an abnormal mucociliary clearance, which is clinically manifested in the patient, presenting symptoms such as repeated respiratory tract infections in children, cases of infertility in men and women by affecting the movement of spermatozoa and ciliary movement of the uterine tubes, respectively.[4-6] Likewise, cases have been reported with clinical presentation from the neonatal period with atelectasis and recurrent respiratory infections, accompanied in 50% by *situs inversus*.

Pathologies such as cystic fibrosis, immunodeficiencies, pulmonary aspiration, asthma and recurrent respiratory tract infections (sinusitis, otitis, rhinopharyngitis, pneumonias, among others) are part of the differential diagnosis; however, four key features have been identified for the diagnosis of PCD: 1) productive (wet) cough throughout the year; 2) non-seasonal daily rhinosinusitis with early onset; 3) 80% history of respiratory distress syndrome at birth; and 4) laterality defects.[7]

Three cases of patients diagnosed with FCD by electron microscopy are presented below.

PRESENTATION OF CASES

Case 1: eight-year-old female with a history of recurrent respiratory tract infections since birth, three events of pneumonia, two of influenza and three cases of otitis. A diagnosis of asthma was made by spirometry with mild obstruction with positive response to bronchodilator, persisting with productive wet cough despite high doses of asthma control treatment. Recurrent wheezing and coarse ralescence. High resolution chest tomography (HRCT) was performed with the presence of cylindrical bronchiectasis *(Figure 1A)*, pathologies such as cystic fibrosis, immunodeficiencies, gastroesophageal reflux and bronchopulmonary aspergillosis were ruled out. Flexible bronchoscopy was performed for cilia biopsy (endobronchial), which was reported with endobronchial epithelium with ultrastructural and membrane alterations compatible with ciliary dyskinesia (processed by electron microscopy), with absence of dynein arms that corresponds to type I FCD according to the classification of Barlocco and collaborators[8] *(Figure 1B)*. The genetics service performed a molecular panel study of 538 genes by next-generation sequencing for ciliopathy, which reported that the patient is compound heterozygous for two variants in the DNAH5 gene, the variant c.2578-2A>T is previously reported as pathogenic; the variant c.1981C>A (p.Arg661Ser) is classified as of uncertain significance *(Figure 1C)*. Diagnosis of PCD was established and, with it, inhaler dose reduction until withdrawal; pulmonary rehabilitation therapy and multidisciplinary management with otorhinolaryngology, audiology and pediatric cardiology services was initiated. *Situs inversus* was ruled out.

Case 2: 16-year-old female, with repeated respiratory infections since she was three years old, previously treated for difficult to control asthma, all her spirometries showed mild obstruction with no response to bronchodilator; she was approached due to persistent respiratory symptoms (productive cough, abundant secretions in the airway and recurrent wheezing). CT scan showed the presence of cylindrical bronchiectasis *(Figure 2A)*. Flexible bronchoscopy was performed with endobronchial biopsy for electron microscopy, in which changes compatible with type V PCD of the Barlocco and collaborators classification,[8] corresponding to ciliary fusion, were reported *(Figure 2B)*. A ciliopathy genetic panel was requested, which showed heterozygous deletion of chromosome 16p12.2 pathogenic

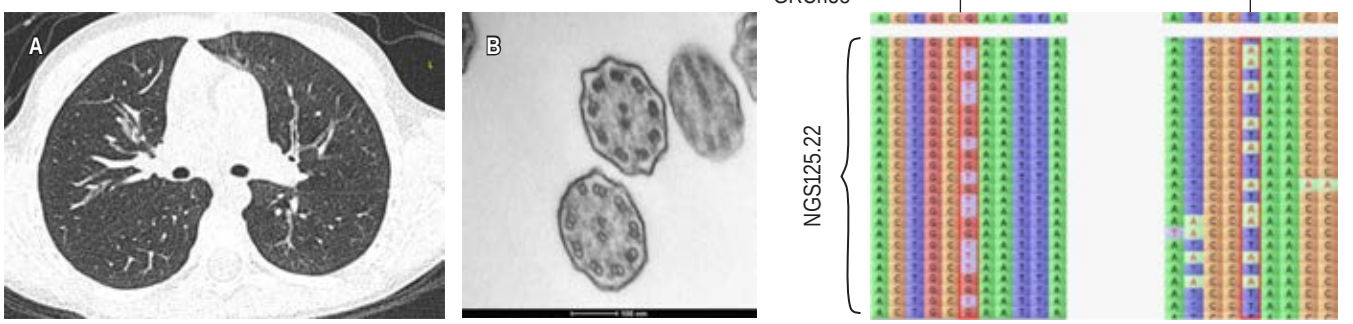

Figure 1: A) Axial section of high-resolution pulmonary computed tomography, showing cylindrical bronchiectasis in the right hemithorax; electron microscopy **(B)** shows absence of dynein arms. Primary ciliary dyskinesia type I according to the modified classification of ciliary alterations by Barlocco et al.[8] The genetic study **(C)** reported two variants in the DNAH5 gene, the variant c.2578-2A>T and the variant c.1981C>A (p.Arg661Ser).

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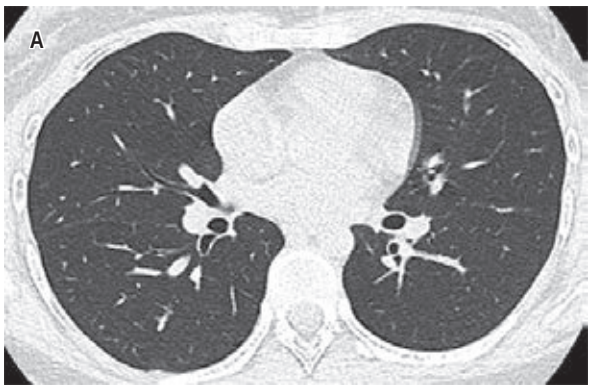
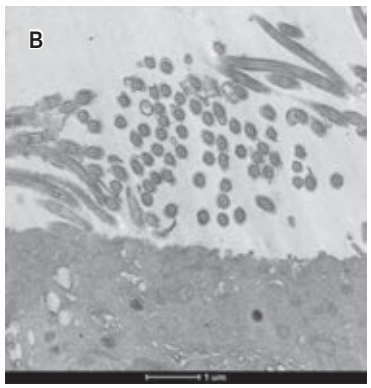
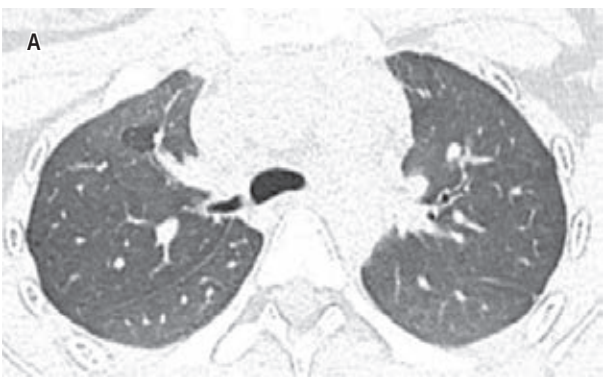




C

Detected change	Chromosomic location	Genomic coordinates	Genes located in the region	CNV Type
Heterozygous deletion	16p12.2	Chr16:21477979- 21808586	IGSF6, METTL9, OTOA	Pathogenic variant

Figure 2: A) Axial section of high-resolution computed tomography showing cylindrical bronchiectasis in the right lung and peribronchial thickening in the left lung; electron microscopy **(B)**, showing changes compatible with primary ciliary dyskinesia type V of the Barlocco *et al* classification,[8] corresponding to ciliary fusion; genetic panel **(C)** of ciliopathies with heterozygous deletion of chromosome 16p12.2 pathogenic variant.
CNV = copy number variation.



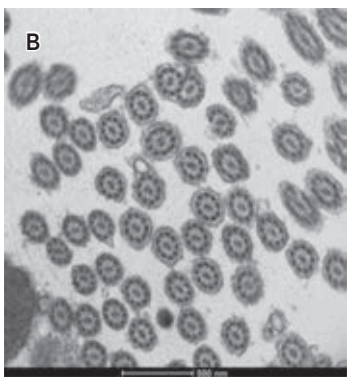


Figure 3:

A) Axial section of high-resolution computed tomography of the chest, showing peribronchial thickening at the hilar level in both lung fields; electron microscopy **(B)** shows absence of peripheral doublets and fusion in some of the cilia membranes, corresponding to primary ciliary dyskinesia type III of the Barlocco *et al* classification.[8]

variant *(Figure 2C)*. Pulmonary rehabilitation therapy was started, inhaler doses were reduced until withdrawal, with improvement of respiratory symptoms. Currently, she is only undergoing pulmonary physiotherapy. Multidisciplinary management was initiated through genetics, cardiology and otorhinolaryngology services. *Situs inversus* was ruled out.

Case 3: 14-year-old female with a diagnosis of chronic cough and suppurative syndrome. At birth she presented airway infection. During her childhood with recurrent infections of pharyngotonsillitis, repeated otitis media, surgical treatment of tonsillectomy and placement of ventilation tubes; thrive failure. She presented recurrent events of bronchospasm, productive cough, without requiring hospitalization. CAT scan was requested, with presence of bronchiectasis and peribronchial thickening *(Figure 3A)*, spirometry with normal bronchodilator without reversibility, esophagogastroduodenal series with grade I reflux. Bronchoscopy was performed with endobronchial biopsy for electron microscopy; it reports alterations compatible with PCD, with alteration in the microtubules, absence of peripheral doublets *(Figure 3B)*, PCD type III of the Barlocco and collaborators classification.[8] Genetic panel is requested.

DISCUSSION

Most patients with SCD present with clinical manifestations at an early age; however, diagnosis is delayed until an average age of four to six years secondary to the low index of suspicion.[9] In order to make a diagnosis at an earlier age, this pathology should be suspected in patients with recurrent or chronic respiratory symptoms such as wet

cough, rhinorrhea, sinusitis, otitis media and/or presence of bronchiectasis, with a history of term newborn with admission to the Neonatal Intensive Care Unit due to pulmonary pathology, congenital heart disease or alterations of laterality.[10] In our case series, we observed that all three patients presented recurrent respiratory tract infections, initially treated as difficult-to-control asthma. Likewise, 100% presented radiological alterations such as peribronchial thickening and bronchiectasis; CATAR was used in all cases.

There is no single diagnostic test for the diagnosis of PCD; therefore, predictive scales such as PICADAR, used in combination with different study methods, have been proposed. In our institution we have flexible bronchoscopy, so it was decided to perform the diagnosis by this method; the interpretation by electron microscopy was subrogated to the National Institute of Medical Sciences and Nutrition «Salvador Subirán», since there are few centers that have this resource. Our institution has a genetics service, so a molecular study for ciliopathies was requested. At present, other methods exist in specialized centers, such as the exhaled nitric oxide fraction; however, in our center, we do not have this resource, which is a limitation for this study.

Among the complementary studies to measure pulmonary function, spirometry with bronchodilator was requested, which may be normal during early childhood, reaching, according to the evolution of the condition, a certain degree of airflow obstruction.

At present, there is no treatment to correct ciliary dysfunction. Consistent treatment is pulmonary physiotherapy to improve mucociliary clearance and avoid bacterial superinfection, so early initiation of antibiotic therapy is recommended for respiratory tract infection.[11] Multidisciplinary management is important.

CONCLUSIONS

Patients with PCD present a variable clinical picture, with mild to moderate manifestations, usually with early onset and late diagnosis, affecting the patient's quality of life. As it is an autosomal recessive pathology, genetic counseling is required for the parents, since there is no definitive treatment to recover the movement of the affected cilia. In our study it was observed that we still have limitations to achieve an early diagnosis due to the heterogeneity of the symptoms and the lack of resources, such as electron microscopy and exhaled nitric oxide fraction, but it is extremely important to apply scales of diagnostic suspicion and to start early the approach to rule out other pathologies. We plan to apply the study and prospectively follow up to these patients in order to have a better knowledge of prognosis and quality of life.

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Conflict of interests: the authors declare that they have no conflict of interests.

NCT
Neumología y Cirugía de Tórax
Vol. 82 - No. 1 / January-March 2023

Clinical case
doi: 10.35366/114229

Pancreaticopleural fistula, a rare complication of pancreatic pseudocyst. Presentation of two cases

Fístula pancreaticopleural, una rara complicación del pseudoquiste pancreático. Presentación de dos casos

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ABSTRACT. The presence of pancreaticopleural fistula is a rare complication of acute or chronic pancreatitis, and it can also occur in cases of pancreatic trauma. We report two cases of pancreatic pseudocyst that communicates towards the left hemithorax, both males aged 39 and 27 who, as a history, refer to intense chronic alcoholism. They present with long-term chest pain and dyspnea; pleural effusion is documented in imaging studies. When the endopleural tube is placed, the effusion appears dark and persists with a high output; when carrying out a study of the pleural fluid chemistry, a considerable elevation of pancreatic enzymes is identified, for which reason they are operated on by left posterolateral thoracotomy. A transdiaphragmatic fistula was identified in the first case and a transhiatal fistula in the second. In both cases, drainage plus lavage and decortication with closure of fistulas and placement of pleural drainage were performed. Both patients presented favorable evolution without requiring another procedure.

Keywords: pancreatic pseudocyst, pancreatic pleural fistula, pancreatitis, pleural effusion.

RESUMEN. La presencia de fístula pancreaticopleural es una rara complicación de pancreatitis aguda o crónica, asimismo, puede llegar a presentarse en casos de trauma pancreático. Reportamos dos casos de pseudoquiste pancreático que se comunica hacia hemitórax izquierdo, ambos masculinos de 39 y 27 años, quienes, como antecedente, refieren alcoholismo crónico intenso. Se presentan con dolor torácico de larga evolución y disnea; se documenta derrame pleural en estudios de imagen. Cuando se coloca el tubo endopleural, el derrame aparece oscuro que persiste con un gasto elevado; al realizar estudio de la química de líquido pleural, se identifica elevación considerable de enzimas pancreáticas, por lo que son intervenidos por toracotomía posterolateral izquierda. Se identifica fístula transdiafragmática en el primero de los casos y transhiatal en el segundo. En ambos casos, se realizó drenaje más lavado y decorticación con cierre de fístulas y colocación de drenaje pleural. Ambos pacientes presentaron evolución favorable sin requerir otro procedimiento.

Palabras clave: pseudoquiste pancreático, fístula pancreaticopleural, pancreatitis, derrame pleural.

INTRODUCTION

The presence of pancreaticopleural fistula (PPF) is a rare complication of chronic, acute pancreatitis or pancreatic trauma. The contents of a pancreaticopleural fistula can enter the thoracic cavity through the esophageal hiatus, the costodiaphragmatic angle and even through the diaphragm.[1-3] Pleural effusion may occur in patients with acute pancreatitis in up to 9%; other pulmonary complications of acute or chronic pancreatitis are pneumonitis, atelectasis, dyspnea with respiratory distress.[4-6] Cases of PPF have been described in only 0.4% of patients with pancreatitis and in up to 4.5% of those with pancreatic pseudocyst, especially in those associated with alcoholism.[1,4,6] The most commonly described symptoms are dyspnea, chest pain and cough of chronic manifestation,

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Received: IV-11-2023; accepted: VIII-09-2023.

How to cite: Hernández-Padilla SL, Inocencio-Ocampo AE, Vázquez-Minero JC. Pancreaticopleural fistula, a rare complication of pancreatic pseudocyst. Presentation of two cases. Neumol Cir Torax. 2023; 82 (1): 42-45. https://dx.doi.org/10.35366/114229

as well as the presence of pleural effusion, which is more frequent on the left side.[7-9] The mechanism occurs in the presence of a well-demarcated or ruptured pseudocyst, or a pancreatic duct where enzymatic activity smoothes the tissues, which favors a pleuroperitoneal communication that transforms into a fistula from the cyst into the pleural cavity.[8-10] Extremely high pleural fluid amylase levels (> 50,000 IU/L) in addition to imaging studies in correlation with the patient's clinical presentation should suggest the presence of PPF.[9,10] The endoscopic retrograde cholangiopancreatography approach has been described for the treatment of PPF, as well as the thoracic approach.[10]

We present two cases that were approached by thoracotomy with drainage, lavage and decortication, in addition to the use of postoperative endopleural probes, which achieved remission in both patients.

PRESENTATION OF CASES

Clinical case 1. 39-year-old man, with a history of chronic alcoholism, with episodes of recurrent abdominal pain. His condition began three months prior to his admission, with pleuritic pain in the left hemithorax, progressive dyspnea and attack to the general condition; a chest X-ray was taken in which pleural effusion was identified. A thoracentesis was performed and a thick, dark pleural fluid was obtained, which, upon cytological and cytochemical analysis, showed amylase levels of 16,043 U/L and Light criteria for neutrophilic exudate. Subsequently, on performing computed axial tomography (CT) of the thorax and abdomen *(Figure 1A)*, free fluid communication of the abdomen with the left hemithorax was identified, so it was decided to take the patient to the operating room to perform posterolateral thoracotomy; Parietal pleura was found to be 8 mm thick and visceral pleura 5 mm thick, abundant fibrin material and pus in the cavity, a fistulous tract between the abdominal cavity and left diaphragm of 1 cm in diameter *(Figure 1B)*, with a collection of 100 mL of whitish liquid. Lavage and decortication were performed until adequate pulmonary expansion was achieved, the fistulous tract was debrided; edges were identified and the defect was closed with nonabsorbable 2/0 polypropylene suture *(Figure 1C)*; pulmonary reexpansion was verified. After the treatment, the patient had an adequate clinical evolution; the endopleural drains, with serohematic output that decreased until their removal five days after the procedure. A control CT scan was performed, which showed a decrease in the initial pancreatic collection. After evaluation by the Gastroenterology Service, conservative management was left. At six months of surveillance with CT of the thorax, without evidence of complications.

Clinical case 2. A 27-year-old man with a history of alcoholism since he was 14 years old and episodes of abdominal pain since one year prior to the assessment, for which he sought hospital care. He reported progressive dyspnea and increased abdominal pain, in addition to chest pain. Chest CT scan was performed and reported left hemithorax occupation associated with massive pleural effusion, with displacement to the right of mediastinal structures *(Figure 2A)*. A left endopleural tube was placed, which, after placement, persists with an output of approximately 600 mL daily for two weeks, with a dark appearance and liquid consistency. He continued with respiratory deterioration, so he was referred to the Thoracic Surgery Area where pleural fluid analysis was requested, which revealed hematic exudate with elevated levels of amylase (195 U/L) and lipase (3,095 U/L). In addition, he showed leukocytosis and thrombocytosis in the blood biometry report. An abdominal CT scan was performed

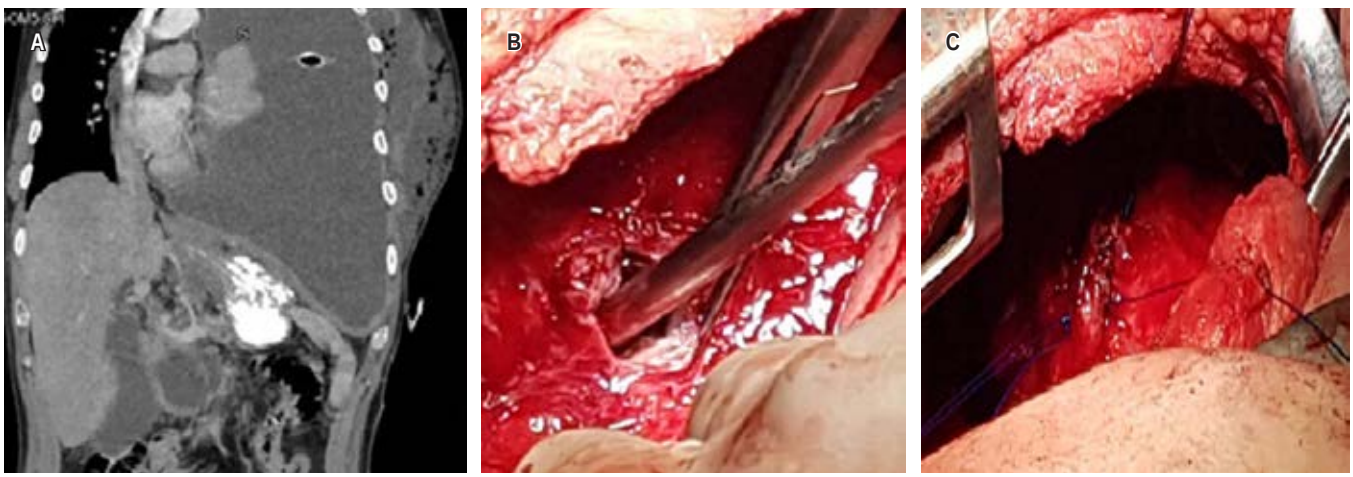

Figure 1: A) CT scan of case 1; shows left pleural effusion. **B)** Fistula site in diaphragm. **C)** Closure of defect with nonabsorbable suture.

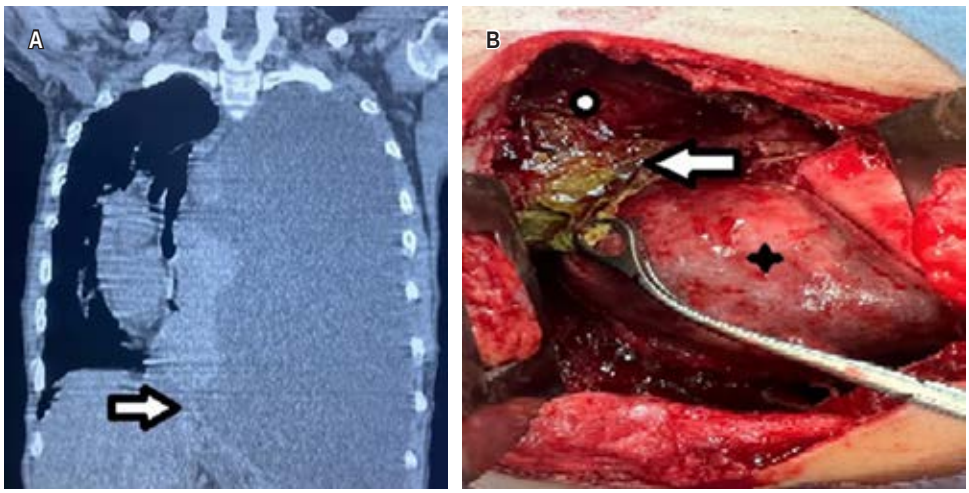

Figure 2:

A) Computed axial tomography of the thorax with massive pleural effusion, the arrow points to the site of the fistula. **B)** Thoracotomy, the site of the fistula marked with the arrow, the dot indicates the diaphragm and the asterisk the left lower lobe.

and a peripancreatic abdominal collection corresponding to pancreatic pseudocyst was identified. It was decided to go to the operating room; lavage and left decortication were performed; pleural effusion secondary to pancreatic pseudocyst communicated to the left hemithorax through the esophageal hiatus, pulmonary trapping, septated pleural effusion and left fibrothorax were identified *(Figure 2B)*. Postoperatively, the pleural drains produced a low output, serohematic appearance (30-100 mL/day); they were removed on postoperative days five and seven. A control CT scan was performed where minimal abdominal collection persisted. After evaluation by the Gastroenterology Service, it was decided to maintain expectant management. The patient had a good postoperative evolution and was discharged on postoperative day 10. Post-surgical follow-up, at one month and three months with simple chest X-ray and at six months with chest CT, there was no evidence of complications.

DISCUSSION

Pancreaticopleural fistula is a rare complication that occurs in patients with pancreatic pathology. Its pathophysiology describes a leaking pancreatic duct or a pseudocyst that can access the pleural cavity through a diaphragmatic hiatus or directly transdiaphragmatic; communication in the costodiaphragmatic angle has also been described.[1]

In our patients, the communication from the pseudocyst to the thorax was transdiaphragmatic and through the esophageal hiatus. There are no clear guidelines for the management of PPF because it is a rare entity; it has been reported that 50% of PPF will close with conservative measures, with subsequent resolution of the effusion.[4,10]

PPF is an infrequent entity and difficult to diagnose because it presents nonspecific clinical manifestations; this generates a delay in diagnosis that requires a high index of suspicion. Some differential diagnoses are: parapneumonic pleural effusion, as well as that associated with neoplasia; the history of alcoholism, young patients and associated abdominal pain, favor the diagnosis. The average time to diagnose PPF is about five weeks.[4,7,10] In the cases we present, in addition to being cases of several weeks of evolution, the presence of persistent dark-colored effusion, the history of alcoholism, the pleural fluid study, as well as the imaging studies, both in the abdominal region and in the thorax, allowed us to reach the diagnosis, which coincides with the type of approach referred to in the literature for this type of patients.[1,4,7,10]

As mentioned, in most cases, treatment is conservative without requiring any surgical intervention to the thorax. There are options for the management of these patients as described in a series of four cases reported by Munirathinam M and collaborators in India, which were resolved by endoscopic management of the pancreatic pseudocyst, total parenteral nutrition therapy, octreotide and thoracic drainage with favorable results without requiring thoracic surgery.[8-10]

Surgical treatment is indicated in case of failure of medical treatment (3-4 weeks are considered) or obstruction of the pancreatic duct. Or, when there are loculated effusions that cannot be resolved by placement of thoracic drainage. Operative mortality is 3 to 5%. Recurrence has been reported in up to 11% of cases. The long-term outcome is good in 80-95% of cases, with an overall PPF mortality of 5%.[1,7,9,10]

In our cases, the lack of response to treatment and the long evolution of these cases led to the decision of surgical management. Washing, decortication and dismantling of the fistula were the basis for its successful resolution with a shorter evolution of two weeks in comparison with stays of three and up to six weeks after treatment.[1,4,9,10]

CONCLUSIONS

Pancreaticopleural fistula is a rare and difficult to diagnose complication, requiring a well performed study protocol combined with high suspicion of this entity, CT of the thorax and abdomen, as well as pleural fluid including pancreatic enzyme values.

Surgical management is a resource that should be considered in cases that do not respond to endoscopic management of the pseudocyst, or in patients with thoracic complications that require surgical approach.

Acknowledgments

To the sub directorate of Surgery and the head of the Cardiothoracic Surgery Service of the National Institute of Respiratory Diseases Ismael Cosío Villegas, Mexico City.

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Conflict of interests: the authors declare that they have no conflict of interests.

NCT
Neumología y Cirugía de Tórax
Vol. 82 - No. 1 / January-March 2023

Clinical case
doi: 10.35366/114230

Airway management in a patient with necrotizing cervical fascitis

Manejo de la vía aérea en un paciente con fascitis necrosante cervical

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ABSTRACT. Necrotizing fasciitis is an aggressive skin and soft tissue infection that can rapidly spread through the perifascial planes. It has a high morbidity and mortality and requires aggressive surgical treatment initially to reduce associated morbidity and mortality. The case of a 53-year-old male with a history of diabetes *mellitus* II who presents a cervical abscess after a tonsillectomy, it evolves to cervical and thoracic fasciitis, drainage of the abscess and open tracheostomy are performed in another hospital. He came to our institute with a dehiscent wound, discharge of purulent material, and air leakage from the tracheostomy site. During the procedure, a 4 cm orifice is identified on the anterior wall of the trachea, debridement and placement of negative pressure therapy is performed. Subsequently, a flap is mobilized over the tracheal orifice, and a Montgomery cannula is placed to close the cervical wound. Control bronchoscopy shows a good tracheal lumen, without stenosis or air leak. It is important in a patient with necrotizing fasciitis to have aggressive surgical treatment initially, taking care of the following principles: adequate drainage of all collections, and debridement of all necrotic tissue and taking care not to contaminate adjacent structures.

Keywords: trachea, fasciitis, Montgomery.

RESUMEN. La fascitis necrosante es una infección de piel y tejidos blandos agresiva que rápidamente puede extenderse por los planos perifasciales. Tiene alta morbimortalidad y requiere tratamiento quirúrgico agresivo de forma inicial para disminuir la morbimortalidad asociada. Se expone el caso de un masculino de 53 años con antecedente de diabetes *mellitus* II, que presentó un absceso cervical posterior a una amigdalectomía, evolucionó hasta presentar fascitis cervical y torácica. En otro hospital se le realizó drenaje del absceso y traqueostomía abierta. Acude al instituto con herida dehiscente, salida de material purulento y fuga aérea por sitio de traqueostomía. Durante el procedimiento se identificó orificio en cara anterior de la tráquea de 4 cm, se le realizó desbridamiento y colocación de terapia de presión negativa. Después se movilizó un colgajo sobre orificio traqueal y se colocó cánula de Montgomery para cierre de herida cervical. La broncoscopia de control mostró buena luz traqueal, sin estenosis o fuga aérea. En el paciente con fascitis necrosante es importante un tratamiento quirúrgico agresivo de forma inicial, preservando los siguientes principios: drenaje adecuado de todas las colecciones y desbridamiento de todo el tejido necrótico cuidando no contaminar estructuras adyacentes.

Palabras clave: tráquea, fascitis, Montgomery.

INTRODUCTION

Necrotizing fasciitis is a severe infection of the skin and soft tissues, which causes tissue necrosis and can spread rapidly through the fascial planes.[1] The incidence of this infection varies according to reports from different regions, being more frequent in developing countries, the incidence can be up to 1 in 100,000.[1] It is usually a polymicrobial infection, which makes adequate antibiotic treatment difficult, in addition to the fact that it spreads rapidly through the tissues. Symptoms are very varied and are related to the affected area and the patient's septic process.

The fundamental pillar of treatment is surgical drainage and debridement, which should always be complemented by adequate resuscitation of the patient and coverage with broad-spectrum antibiotics.[2] Cervical infection commonly

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Received: VI-21-2023; accepted: IX-27-2023.

How to cite: Martínez-Sánchez DJ, Waldo-Hernández LI, Palomares-Capetillo P, Vázquez-Minero JC. Airway management in a patient with necrotizing cervical fascitis. Neumol Cir Torax. 2023; 82 (1): 46-48. https://dx.doi.org/10.35366/114230

Neumol Cir Torax. 2023; 82 (1): 46-48

caused by an odontogenic process carries a high morbidity due to the structures present such as large vessels, digestive tract and airway, in addition to the risk of extension to the mediastinum. Therefore, an adequate initial management, preserving these structures, is fundamental to improve the morbimortality of these patients.[3]

CASE PRESENTATION

Male, 53 years old, with diabetes mellitus II with treatment, adequate controls and a smoking rate of 12 packs/year. He refers that approximately 10 days before his admission to the Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, he underwent tonsillectomy which was complicated by a peritonsillar abscess and evolved with cervical and superficial thoracic fasciitis. Abscess drainage was performed with submandibular and cervical approach, placing tracheostomy cannula to ensure airway. She came to our institute presenting wound dehiscence, purulent material leakage, erythema in adjacent tissues and area leakage through the tracheostomy site *(Figure 1A)*.

The wound was debrided and washed, a 4 cm hole was identified in the anterior face of the trachea *(Figure 1B)* and abundant purulent material. It was decided to replace the tracheostomy cannula and negative pressure therapy *(Figure 1C)*. Subsequently, three reexchanges were performed, partially closing the wounds. To ensure and achieve closure of the trachea while maintaining an adequate lumen, it was decided to place Montgomery cannula and mobilize on the same sternocleidomastoid flap, achieving total closure of the wound. Then, on an ambulatory basis, the patient was decannulated and revision bronchoscopy was performed, observing an adequate tracheal lumen, with no evidence of fistula or air leak *(Figure 2)*.

DISCUSSION

Necrotizing fasciitis, as previously mentioned, presents high morbimortality and is associated with a large number of complications. Treatment should be timely and aggressive, taking into account the following points: broad-spectrum antibiotic therapy, aggressive surgical debridement in the first 24 hours, adequate airway management and constant re-evaluation of the patient.[3]

In the past, it was believed that performing a tracheostomy in patients with significant cervical infection was the ideal management to secure the airway and adequately ventilate patients; however, this procedure increases morbidity and presents long-term complications. The infectious process could more easily spread to the mediastinum and poor tracheostomy cannula placement can lead to long-term stenosis.[4] Today, with the development and availability of technology, video laryngoscopy or bronchoscopy can be used to assist in intubation and preserve tracheal integrity.

Many times, due to the extent of the infectious process and tissue necrosis, extensive debridement is necessary, resulting in large defects of the skin and underlying tissues. Multiple articles have compared in-hospital stay, number of re-interventions and wound evolution using simple cures versus negative pressure therapy, favoring the latter.[5] Therefore, its use is recommended to improve tissue healing and allow early wound closure.

Likewise, when there is a large lesion or defect in the airway, either secondary to an infectious process or as a complication of a procedure, it is important to be able to reconstruct and maintain its integrity to ensure adequate ventilation and improve patient morbidity. In this case it was decided to use a Montgomery cannula, which is normally used for tracheal stenosis not candidates for surgical treatment; nevertheless, due to its characteristics, it allowed to ensure the patient's ventilation and phonation, as well as to provide adequate support to mobilize a flap and allow granulation and closure.[6,7]

CONCLUSIONS

It is important to timely diagnose a soft tissue infection in the cervical region and to offer adequate treatment from

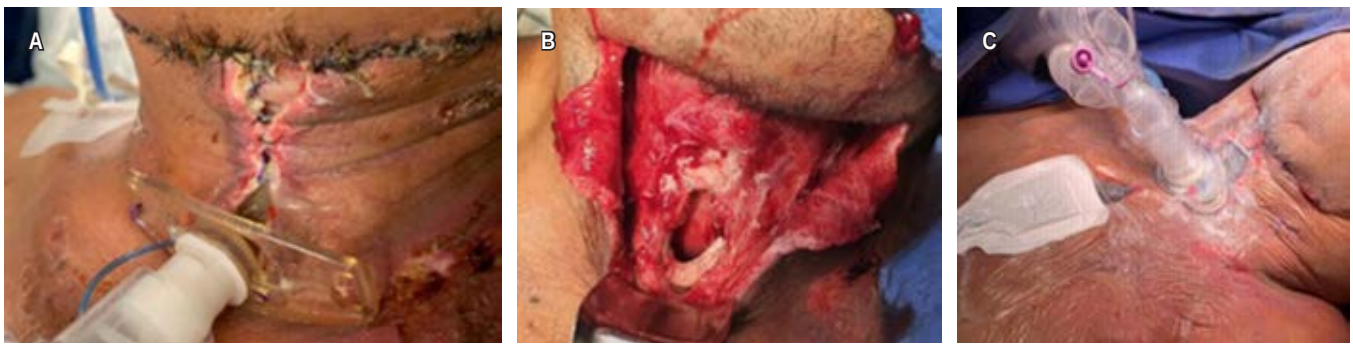

Figure 1: A) Dehiscent cervical wound with purulent material. **B)** Orifice in the anterior face of the trachea of 4 cm. **C)** Result after the first intervention.

Contenido

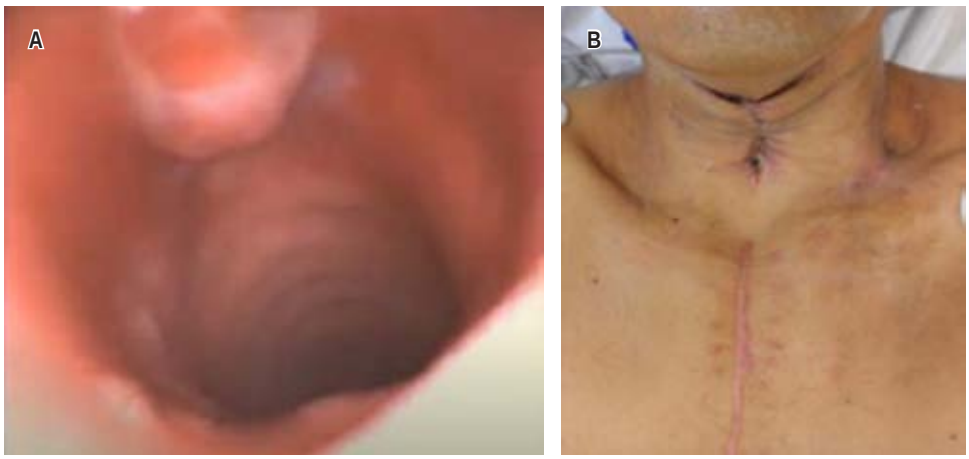

Figure 2:

A) Revision bronchoscopy, scarce granulation tissue in anterior face without stenosis. **B)** Review in the office, adequate closure of all wounds is observed.

the first intervention. This will give the patient the best opportunity to reduce the number of re-interventions, reduce the morbidity associated with the condition and the procedure, and facilitate the resolution of the septic process. In the absence of the equipment or expertise to manage these cases, it is important to consult or refer to the appropriate service or institution. As stated in the literature, and in this case, the use of negative pressure therapy is essential for the treatment of these wounds, the integrity of the trachea should be preserved whenever possible.[8] Providing timely comprehensive management and using all available resources can reduce the morbidity and mortality associated with this condition.[7,9,10]

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Conflict of interests: the authors declare that they have no conflict of interests.

NCT
Neumología y Cirugía de Tórax
Vol. 82 - No. 1 / January-March 2023

Clinical case
doi: 10.35366/114231

Extragonadal mixed germ cell tumor primary of the mediastinum. Case report

Tumor de células germinales mixtas extragonadal primario del mediastino. Reporte de caso

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ABSTRACT. Germ cell tumors are usually neoplastic located in the testicles or ovaries manifested in early life. Extragonadal germ cell tumors are infrequent, representing 1 to 3% of extragonadal germ cell neoplasms. When they present, they are usually 1 to 2 excisions, the anterior mediastinum representing the most common site. They are usually asymptomatic in 20-40% of patients until there is compression or obstruction of nearby structures and there are no symptoms. We present the case of a 22 year old male without comorbidities who started with cough without hourly predominance, hemoptysis, fever, unintentional weight loss, diaphoresis, orthopnea, physical examination revealed pleuropulmonary condensation syndrome, cabinet studies were performed. initially chest X-ray confirmed by tomography chest, abdomen, pelvis, testicular ultrasound and serum studies a mass in the mediastinum located in the anterior compartment, a biopsy was taken and removal of the mediastinal mass, concluding in a primary extragonadal tumor of mixed germ cells of the mediastinum composed of three cell excisions, representing a diagnostic challenge due to their large size. were re offered treatment with chemotherapy based on bleomycin, etoposide, and cisplatin in four cycles without new relapses.

Keywords: mixed germ cell tumor, alpha-fetoprotein, mediastinum.

RESUMEN. Los tumores germinales suelen ser neoplásicas ubicadas en testículos u ovarios, manifestadas en edades tempranas de la vida. Los tumores extragonadales de células germinativas son infrecuentes, representan de 1 a 3% de las neoplasias germinales; cuando se presentan, generalmente son de una a dos estirpes, el mediastino anterior es el sitio más común. Suelen ser asintomáticos en 20-40% de los pacientes; hasta que hay compresión u obstrucción de las estructuras cercanas existe sintomatología. Presentamos el caso de un varón joven de 22 años sin comorbilidades, quien inició con tos sin predominio de horario, hemoptisis, fiebre, pérdida de peso no intencionada, diaforesis, ortopnea. A la exploración física destacaba síndrome pleuropulmonar de condensación; se realizaron estudios de gabinete, al inicio radiografía de tórax confirmando por tomografía de tórax, abdomen, pelvis, ultrasonido testicular y estudios séricos, masa en mediastino localizada en compartimiento anterior. Se realizó toma de biopsia y extirpación de masa mediastinal; concluye en un tumor extragonadal de células germinales mixtas primario de mediastino compuesto por tres extirpes celulares, representando un reto diagnóstico por su gran tamaño. Se ofreció tratamiento con quimioterapia a base de bleomicina, etopósido, cisplatino en cuatro ciclos, sin nuevas recaídas.

Palabras clave: tumor germinal mixto, alfafetoproteína, mediastino.

INTRODUCTION

Primary mediastinal germ cell tumors are rare neoplasms, which have been found to be due to malignant transformation of germ cells that migrate during embryogenesis. In these tumors there is an alteration of the epiblast in its migration and descent, leading to the formation of a late mediastinal tumor.[1,2]

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Received: VII-18-2023; accepted: IX-27-2023.

How to cite: Sánchez-Zazueta E, Miyagui-Adame KA, Gamez-Sainz IL, Galaviz-Humo J. Extragonadal mixed germ cell tumor primary of the mediastinum. Case report. Neumol Cir Torax. 2023; 82 (1): 49-52. https://dx.doi.org/10.35366/114231

They are divided into two groups: seminomatous and nonseminomatous germinal tumors. Seminomas represent 30%, while nonseminomatous represent 70%, subdivided into mature teratomas with 44%, immature teratomas 6%, yolk sac tumors 60%, tumors derived from primitive embryonic cells, representing embryonal carcinoma 5%, tumors of extraembryonic differentiation such as choriocarcinoma 2%.[1,2]

The germinal locations described as extragonadal at the level of the mediastinum are rare, representing 1 to 3% of the extragonadal germinal neoplasms, 1.27 cases per 1'000,000 inhabitants are found without evidence of a primary testicular tumor; another location is the retroperitoneum.[3-5]

At the time of diagnosis, 20-40% of patients are asymptomatic. The initial diagnostic methods are testicular ultrasound to rule out primary gonadal origin, followed by tomographic extension study including chest, abdomen and pelvis. Tumor markers such as alpha-fetoprotein and human gonadotropin are not diagnostic alone, but are useful to guide prognosis. Biopsy is the diagnostic study of choice; when performing it, immunohistochemistry with markers such as OCT4, SALL4 should be requested to confirm the origin of cells as they have high sensitivity for primary mediastinal seminomas and embryonal carcinomas; in cases where the histological diagnosis is not conclusive, karyotyping can be performed in order to identify p12 isochromosomes, which is a cytogenetic anomaly of tumors with germ lineage.

Current recommended treatments of choice are chemotherapy followed by resection of the residual mass. Chemotherapy schedules are similar to those used in tumors of testicular origin with cisplatin-based chemotherapy achieving long-term complete remissions in 50% of cases. The most commonly employed chemotherapeutic scheme includes three to four cycles of cisplatin in combination with etoposide and bleomycin. If after completion of chemotherapy treatment, imaging tests reveal persistence of residual masses, optimal resection of these is usually indicated; up to 30% of primary mediastinal germ cell tumors may show tumor remnants, and suboptimal resection is useful in these cases. When relapse or refractoriness to initial treatment occurs, current salvage chemotherapy regimens are based on paclitaxel or ifosfamide in combination with cisplatin.[6,7]

Due to the infrequency of extragonadal disease we consider this report relevant, even more so because it is a young patient and a mixed germinal tumor in a greater proportion of endodermal sinus; there are very few cases described in the literature, those reported are usually teratomas and the mixed mediastinal variety.

CLINICAL CASE

22-year-old male with no chronic degenerative history. He started with a non-cyanotic, non-emitting cough. After two months of evolution he went to the doctor where viral infection was suspected; two weeks later he persisted with cough accompanied by hemoptysis, orthopnea, nocturnal diaphoresis, weight loss of 7 kg in three months, fever of 39°C. When the symptoms did not improve, a chest X-ray was performed, finding incidentally a mediastinal mass. Subsequently, tomography of the chest, abdomen and pelvis revealed an anterior mediastinal tumor measuring 14 × 13 cm in the right hemithorax, with displacement of mediastinal structures towards the left hemithorax. Because of age and form of presentation, lymphoma was suspected *(Figure 1A)*. Physical examination was compatible with a pleuropulmonary condensation syndrome; a 5 mm right inguinal adenopathy, indurated and immobile, was also found. Labs were requested, highlighting grade 2 anemia, platelets 622,000/mm^3, lactate dehydrogenase 645 u/L, leukocytes 9,000/mm^3, glucose 92 g/dL, creatine 0.9 mg/dL, albumin 3.9 g/dL, negative viral panel, tumor markers with result alpha-fetoprotein 3,080 ng/mL, carcinoembryonic antigen 0.98 ng/mL, human chorionic gonadotropin

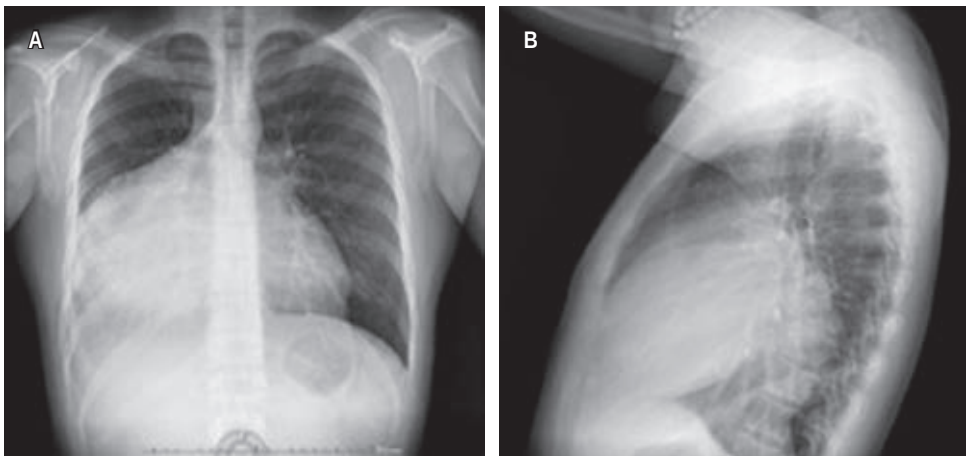

Figure 1:

A) Anteroposterior radiograph.
B) Left lateral chest with radiopacity, showing a mediastinal mass measuring 12 × 10 cm.

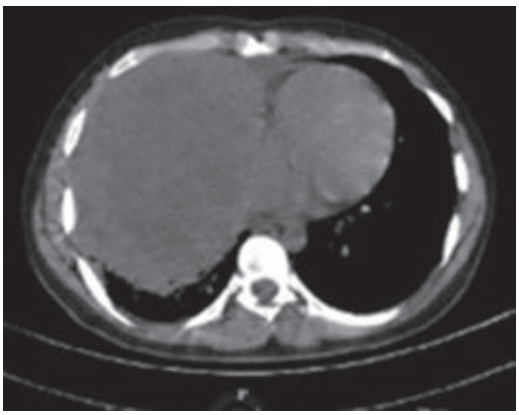

Figure 2: Chest CT simple axial window with a hyperdense mass in the right hemithorax, occupying almost its entirety.

hormone 0.78 ng/mL. Testicular ultrasound showed a simple cyst in the head of the left epididymis of 1 mm. During his hospitalization, he underwent mediastinal biopsy for cardiothoracic surgery in conjunction with resection of tumor mass by thoracotomy; during the trans-surgical event he presented massive hemorrhage of 4,000 milliliters with hypovolemic shock grade 4 requiring massive transfusion; resection in fragments of mediastinal mass was achieved *(Figure 1B)*. Post-surgical findings, mediastinal mass of 12 × 10 cm with fragments larger than 1 cm in the thorax because they were adhered to the pulmonary hilum and, representing a greater risk of bleeding, merited placement of a 36 fr right pleural tube. After the suboptimal tumor resection procedure, the cough, orthopnea, hemoptysis and thermal elevations subsided; the patient was discharged after a good clinical evolution *(Figure 2)*. The biopsy findings were compatible with mixed germinal tumor of the endodermal sinus type 70%, seminoma 25%, embryonal carcinoma 5% with extensive tumor necrosis of 50% of the surgical specimen *(Figure 3)*. Immunohistochemistry showed diffuse positive SALL 4, negative OCT3/4, focal positive AFP, focal positive D2-40 (1%), focal positive PLAP (5%), negative CEA-CD30. He was evaluated by the medical oncology service, which granted chemotherapy with bleomycin, etoposide, cisplatin in four cycles; and also follow-up by the pulmonology, cardiothoracic surgery, medical oncology services where, after five months of post-surgical evolution and with control chest CT scan, the patient remains asymptomatic, with follow-up by multidisciplinary outpatient clinic due to risk of compression of surrounding structures and new relapse.

DISCUSSION

Extragonadal germ cell tumors usually debut with chest pain, cough, dyspnea, hemoptysis, fever. Our patient started with this symptomatology to which unintentional weight loss was added; a mediastinal mass was observed on chest X-ray, which is the initial study as part of the approach in patients who debut with cough of unknown etiology and is useful to rule out differential diagnoses, mainly infectious. As part of the protocol, a tomography of extension to the thorax, abdomen and pelvis was performed, which confirmed mediastinal mass; tumor markers were requested for predictive purposes, alpha-fetoprotein elevation suggestive of nonseminomatous tumor was found; suspecting a primary gonadal origin, testicular physical examination and testicular ultrasound were performed to rule out the presence of tumor in this site; a cyst in the epididymis was found in the patient. Due to the absence of tumor in the gonads and the previous tomographic findings in the mediastinum, he was evaluated by the Cardiothoracic Surgery area. He requested a mediastinal biopsy as part of the diagnostic protocol being the gold standard; the result showed a mixed variety germinal tumor composed of endodermal sinus, seminoma, embryonal carcinoma. The next step was immunohistochemistry for confirmation purposes; the immunohistochemistry was compatible with SALL 4, AFP, D2-40, PLAP positive.

The first-line treatment for nonseminomatous germ cell tumors is chemotherapy followed by surgical resection. Currently, the drug of choice for chemotherapy is cisplatin, which achieves complete remission in 50% of cases. The preferred scheme of choice includes three to four cycles of cisplatin at a dose of 20 mg/m^2 combined with etoposide 100 mg/m^2/day for five days and bleomycin 15 mg/m^2 weekly. Once these cycles have been completed,

Figure 3: Mediastinal biopsy of a 12 × 10 centimeter surgical specimen.

monitoring should be carried out with a cabinet study; if the residual mass persists, surgical resection is indicated; when the residual tumor is larger than 1 cm, suboptimal resection is chosen, and when there is no macroscopic residual tumor, optimal resection is considered. During the biopsy, due to the size of the tumor and the parahilar location, suboptimal surgical resection of the tumor mass was performed with subsequent chemotherapy based on bleomycin, etoposide and cisplatin in four cycles, which must be individualized for each patient. After achieving tumor remission with chemotherapy, all patients should be followed up, since up to 50% usually relapse in the first two years. When relapse or refractoriness to treatment occurs, the rescue chemotherapy regimens are paclitaxel 135 to 250 mg/m^2/day every three weeks or ifosfamide 1,200 mg/m^2/day for five days plus cisplatin, monitoring hematologic and nephrologic toxicities. The patient, currently, after five months of evolution, remains asymptomatic after treatment with monthly follow-up, due to the risk of mediastinal mass overgrowth and compression of structures due to the poor prognosis as it is a germinal tumor of three cell lines.[4-10]

CONCLUSION

Extragonadal germinal tumors debut clinically when the disease is advanced due to compression of neighboring structures, so an early histopathologic diagnosis is essential. During the biopsy of the patient, a suboptimal tumor resection had to be performed in the same surgical time, due to the large size and parahilarity of the tumor, with the risk of bleeding. As these tumors were vascularized, the patient had a drainage of 4,000 milliliters, so he had to undergo transfusion and endopleural catheterization; subsequently he had a good evolution. The histopathological result was a mediastinal tumor of mixed germinal variety not previously described in the literature. Treatment must be individualized, being essential to focus on the subtype of germinal tumor; preoperative chemotherapy makes the mediastinal tissues fibrotic and worsens surgical planning, so in this patient tumor resection followed by chemotherapy was of greater benefit.

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Conflict of interests: the authors declare that they have no conflict of interests.

NCT
Neumología y Cirugía de Tórax
Vol. 82 - No. 1 / January-March 2023

Respiratory world

doi: 10.35366/114232

Dr. Jules Arthur Peter Pare. A decade after his departure

Dr. Jules Arthur Peter Pare. A una década de su partida

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How to cite: Sandoval-Gutiérrez JL. Dr. Jules Arthur Peter Pare. A decade after his departure. Neumol Cir Torax. 2023; 82 (1): 53. https://dx.doi.org/10.35366/114232

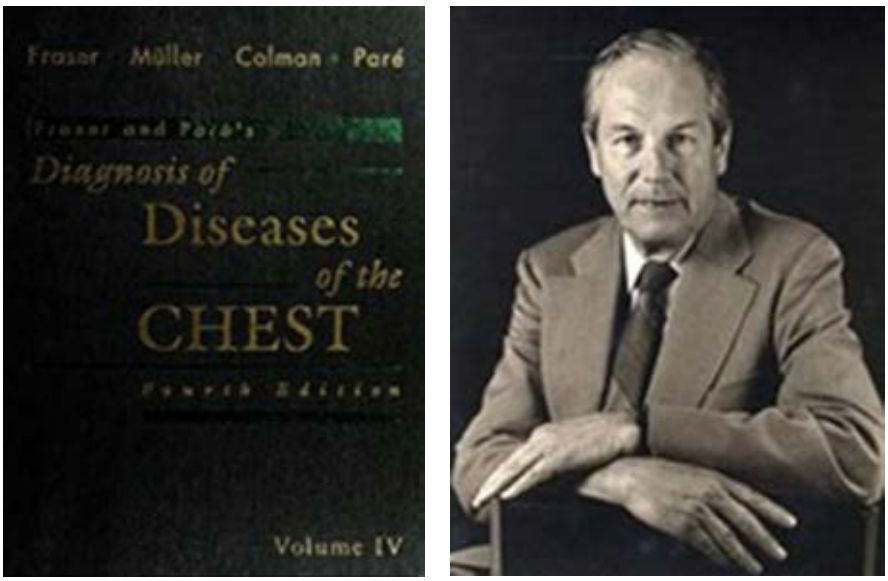

Figure 1: Dr. Peter Paré and his work.
Taken from: Jules PARÉ Obituary. https:/www.legacy.com/us/obituaries/legacyremembers/jules-par-obituary?id=43867623

In 2013, Canadian Pneumologist Dr. Jules Arthur Peter Paré passed away.[1] He was the trainer of several generations of experts in the respiratory system at an international level, he had the vision to articulate physiology, radiology and anatomopathology in the study of the lung *(Figure 1)*. His book was a work of reference for several years; in addition, he was known for being a great clinician and his famous visit passes. His teachings were shared by his two sons: one a pathologist and the other a pulmonologist.

He was the first scientist in the world to propose the use of corticosteroids in the treatment of bronchial asthma. He was a model teacher, gentle, with good humor and a decisive personality, characteristics that we are looking for in these times.

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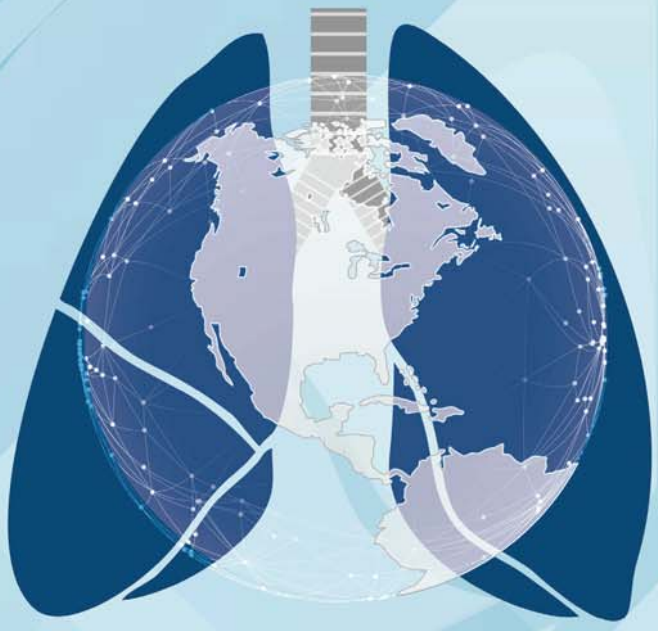

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