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Neumología y Cirugía de Tórax

Asthma control: a challenge in care

ORIGINAL RESEARCH

- Relationship between illness perception, treatment, adherence behaviors and asthma control: a mediation analysis
- Clinical and chest imaging characteristic in patients with COVID-19 in a hospital from Tegucigalpa, Honduras
- Descending necrotizing mediastinitis. A 16-year experience in a referral center

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Richard W Light MD, *in memoriam*.
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Editorial
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Asthma control: a challenge in care

Control de asma: un reto en la atención

María del Carmen Cano-Salas*

*Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico.

Asthma is one of the most common chronic noncommunicable diseases worldwide, affecting about 339 million people in the world.[1] The global prevalence in children and adolescents is estimated at about 10.5%[2] and in adults it is between 6-7%;[3] with regional variations in which low- and middle-income countries show a continuous increase, while in high-income countries it seems to be stabilizing.

Asthma is a disease with a heterogeneous behavior, with mild to severe levels; despite this variability, two domains should always be considered in the evaluation of patients that are very useful for therapeutic decision-making: current control (e.g., symptoms, use of rescue medication and lung function) and future risk (e.g., exacerbations and decreased lung function).

Asthma control refers to the degree to which the manifestations of asthma have been eliminated or diminished due to treatment, according to the control achieved we can speak of the suitability and compliance with the treatment objectives.[4] In recent years, the great advances that have been made in the treatment of asthma, especially in severe asthma with the use of biologic drugs, have led to better control of the disease; however, it is still a challenge to achieve and maintain it.

Factors that may contribute to poor asthma control include: treatment barriers (poor adherence, poor inhaler technique or poor access to medications), comorbidities (e.g., allergic rhinitis, dysfunctional breathing, obesity, vocal cord dysfunction, gastroesophageal reflux disease, chronic rhinosinusitis with nasal polyposis, psychosocial factors, among others), exposure to triggers (e.g. allergens, viruses, tobacco smoke, pollution) and certain inflammatory features such as T2 inflammation and within this, eosinophilia and allergic sensitization.

Around poor asthma control there are several issues that need to be addressed in the same patient, so that multidisciplinary and collaborative care is essential to identify and treat the factors involved.

This issue of NCT includes the work of Lugo-González IV et al., *Relación entre percepción de enfermedad, tratamiento, adherencia y control del asma: un análisis de mediación*;[5] this is a novel work because it includes a model that evaluates disease perception, medication beliefs, adherence to treatment and asthma control through tools validated in the Mexican population. The authors found that psychological factors are predictors of adherence and asthma control; this reinforces that the approach to patients is multidisciplinary and that psychological interventions are indispensable in the treatment of the disease.

Adherence is, among the treatment barriers, a great challenge to overcome; despite having had an effective pharmacological treatment for most patients for several decades, I am referring to inhaled corticosteroids, only 25-30% of patients are adherent. On the other hand, it is well known that there may be discordance between the data provided by patients and what we find when applying objective adherence measurement tests; however, in this study the self-report of adherence to treatment was high, related to patients with a positive perception of the disease and treatment; however, more than 60% were evaluated as non-adherent. This is reflected in the fact that only 51% of patients had control according to the Asthma Control Questionnaire (ACT).

Lack of adherence implies a worse control of the disease and, therefore, a greater impact on the quality of life of patients, as well as on direct and indirect health costs. In addition, it is evident that the causes of poor control are multiple in most patients, which is why addressing the clinical aspects of the condition (symptoms, lung function,

Correspondence:
María del Carmen Cano-Salas, M.D.
Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico.
E-mail: carmencano09@gmail.com

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etc.) are not sufficient in patients with uncontrolled asthma and we must investigate individually the causes that favor poor symptom control.

Another aspect that should be highlighted from the findings of the study is that patients with greater adherence to treatment are those who have a positive perception of treatment; with a high need for treatment and moderate concern for adverse events of the control drugs, this, from my point of view, may be a reflection of the education that patients receive about the disease and at the same time of the confidence in the drugs to improve their health conditions. In this sense, it is important to dedicate exclusive time to inquire about patients' preferences, beliefs and knowledge, so that treatment can be individualized by covering pharmacological and non-pharmacological aspects, including emotional aspects within these.

Asthma is a complex entity that must be approached from different perspectives, which requires the collaborative work of several specialists in the search for and treatment of the factors associated with uncontrolled asthma; likewise, it is necessary that as physicians we strive to provide space for patient education, which is undoubtedly a debt that contributes significantly to the barriers to treatment. At present, we are obliged to seek the best comprehensive strategy for each patient with asthma to achieve control of the disease and reduce the risks associated with this condition.

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Relationship between illness perception, treatment, adherence behaviors and asthma control: a mediation analysis

Relación entre percepción de enfermedad, tratamiento, adherencia y control del asma: un análisis de mediación

Isaías Vicente Lugo-González,* Cynthia Zaira Vega-Valero,* Fabiola González-Betanzos,‡ Susana Robles-Montijo,* Margarita Fernández-Vega§

*Facultad de Estudios Superiores Iztacala. Universidad Nacional Autónoma de México. Tlalnepantla, Estado de México, Mexico; ‡Facultad de Psicología, Universidad Michoacana de San Nicolás Hidalgo. Morelia, Michoacán, Mexico; §Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico City, Mexico.

ABSTRACT. Introduction: the negative illness perception and the treatment is linked to the lack of treatment adherence, as well as negative results in asthma control, two of the main problems in patients with asthma. **Objective:** the aim of the study was to evaluate the mediating role of treatment perception in the relationship between illness perception, treatment adherence, and asthma control. **Material and methods:** a non-experimental cross-sectional correlational study was carried out in which 267 adults with asthma participated (74.2% women, 26% men, X_{age} 45.60 ± 14.34 years). They answered the illness perception questionnaire-revised, the belief about medicines questionnaire, the medication adherence reporting scale-asthma, and the asthma control test. A mediation analysis was performed based on the commonsense model and evaluated through absolute, general, and comparative fit indices. **Results:** the model showed that the illness perception, treatment adherence, and asthma control are mediated by the treatment perception. The model explains 43% of the variance of asthma control, showing an acceptable fit (χ^2 = 34.615, p = 0.002, χ^2/gl = 2.47, RMSEA = 0.074 [90% CI = 0.043-0.106], CFI = 0.937 and TLI = 0.874). **Conclusion:** the model locates psychological predictors of adherence and asthma control, allowing to propose interventions in the clinical context to address the problems of adherence and asthma control.

Keywords: illness perception, treatment perception, treatment adherence, asthma control.

RESUMEN. Introducción: la percepción negativa de la enfermedad y el tratamiento se vincula con la falta de adherencia al tratamiento, así como con resultados negativos en el control del asma, dos de los principales problemas en pacientes con asma. **Objetivo:** evaluar el papel mediador de la percepción del tratamiento en la relación entre percepción de la enfermedad, adherencia al tratamiento y el control del asma. **Material y métodos:** se realizó un estudio no experimental transversal correlacional en el que participaron 267 adultos con asma (74.2% mujeres, 26% hombres, X_{edad} 45.60 ± 14.34 años). Respondieron el cuestionario revisado de percepción de enfermedad, el cuestionario de creencias sobre la medicación, la escala de reporte de adherencia a la medicación-asma y el test de control del asma. Se realizó un análisis de mediación basado en el modelo de sentido común y evaluado mediante índices de ajuste absoluto, general y comparativo. **Resultados:** el modelo mostró que la percepción de la enfermedad, la adherencia al tratamiento y el control del asma están mediados por la percepción del tratamiento. El modelo explica 43% de la varianza del control del asma, mostrando un ajuste aceptable (χ^2 = 34.615, p = 0.002, χ^2/gl = 2.47, RMSEA (error cuadrático medio de aproximación) = 0.074 [IC a 90% = 0.043-0.106], CFI (índice de ajuste comparativo) = 0.937 y TLI (índice de Tucker-Lewis) = 0.874). **Conclusión:** el modelo ubica factores psicológicos predictores de adherencia y control del asma, permitiendo proponer intervenciones en el contexto clínico para abordar los problemas de adherencia y control de la enfermedad.

Palabras clave: percepción de la enfermedad, percepción del tratamiento, adherencia al tratamiento, control del asma.

Correspondence:
Isaías Vicente Lugo-González, MD
Facultad de Estudios Superiores Iztacala. Universidad Nacional Autónoma de México. Tlalnepantla, Estado de México, Mexico.
E-mail: isaiaslugo@iztacala.unam.mx

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Abbreviations:

ACT = asthma control test.
CFA = confirmatory factor analysis.
BC = bootstrapping and bias-corrected model.
BMQ = beliefs about medicines questionnaire-specific.
CFI = comparative fit index.
CSM = common sense model and self-regulation of illness.
NCD = necessity–concerns differential.
COPD = chronic obstructive pulmonary disease.
IPQ-R = illness perception questionnaire-revised.
KSL = Kolmogorov Smirnov-Lilliefors statistic.
MARS-A = medication adherence reporting scale-asthma.
NCF = necessity-concerns framework.
RMSEA = root mean square error of approximation.
SEM = structural equation modeling.
TLI = Tucker-Lewis index.

INTRODUCTION

Negative illness perception and treatment is linked to lack of adherence to treatment, as well as to negative outcomes in asthma control,[1] two of the main problems in patients with asthma, since it is estimated that more than 50% are not controlled and more than 75% are non-adherent.[2,3] Negative illness perception and treatment are considered intentional causes of non-adherence, since based on them, people do not use their treatment or use it inconsistently over time, limiting the achievement of optimal results in disease control.[4] This process has been studied from the common sense model and disease self-regulation (CSM)[5] and the necessity-concerns framework (NCF).[6] These models explain the lack of control as a result of non-adherence behaviors, which would derive from negative perceptions about the disease and the treatment.

The CSM and NCF are process models that are organized in three stages: 1) the perceptual stage, whose sub-dimensions are illness perception and treatment perception; 2) response stage, which are specific behaviors derived from how the disease and treatment are perceived; and 3) outcome evaluation stage, in which adequate or inadequate disease control is observed.[5,6]

Although non-adherence and poor control are common problems in patients with asthma, the evidence should focus on determining the factors that explain them.[2,3] In this regard, research results have shown that necessity of treatment (from the NCF model) better predicts adherence behaviors (OR = 1.742, 95% CI [1.569, 1.934], $p < 0.001$)[7-9] than beliefs about the disease (from the CSM model, r = 0.04-0.13),[10,11] so that the latter has been questioned as a predictor of adherence to treatment;[12] but not of disease control and clinical outcomes (r = 0.13-0.56).[13-15] Based on both models, research studies have focused in particular on explaining adherence and non-adherence behaviors.[9-11,16-18]

Recently, predictive data on asthma adherence and control have been published, considering either the CSM model or the NCF model.[1,19] However, some authors have considered that including variables from both models could have better predictive results,[4,10,20-22] in fact, studies have been proposed in which the treatment perception would function more as a mediating variable between illness perception and adherence behaviors.[22]

Objective. To evaluate the mediating role of the positive effects of treatment perception on the relationship between illness perception, treatment adherence behaviors, and disease control in Mexican patients with asthma.

MATERIAL AND METHODS

Design. A non-experimental, cross-sectional, descriptive and correlational study was carried out with the participation of adults with asthma from the Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas (INER) in Mexico City.

Participants. Non-probabilistic convenience sampling was used. A total of 267 adults with asthma participated, of whom 198 (74.2%) were women and 69 (26%) men, with an average age of 45.6 ± 14.3 years. Participants would have to have a confirmed diagnosis of asthma, indication for controller treatment and no concomitant diagnosis of chronic obstructive pulmonary disease (COPD).

Instruments:

1. Sociodemographic and clinical data questionnaire: set of questions to gather information on personal, family, educational, occupational data and variables related to the disease (time of disease evolution).
2. Illness perception questionnaire-revised (IPQ-R): 14 items were used to assess the positive illness perception (timeline chronic, personal control, coherence and treatment control) of the Mexican version for patients with asthma.[23] The response form of the instrument is defined on a four-point Likert scale (one = strongly disagree, four = strongly agree).
3. Beliefs about medicines questionnaire-specific (BMQ): 10 items were used to evaluate the treatment perception (necessity and concern) of the Mexican version for patients with asthma.[24] The response form of the instrument is defined on a four-point Likert scale (one = strongly disagree, four = strongly agree). According to Horne,[6] a differential necessity-concern score (DNP) is obtained by subtracting the concern score from the need score.
4. Medication Adherence Report Scale-Asthma (MARS-A): five items were used to evaluate the frequency of intentional non-adherence behaviors to the control medication of the Mexican version for patients with asthma.[25] The responses of the instrument are defined

on a four-point Likert-type scale (one = I always do so, to four = I never do so). For the interpretation of results, higher scores on the scale imply a better level of adherence to the control treatment. In categorical terms, a score between five and 19 would correspond to non-adherent patients and a score of 20 to adherent patients.

5. Asthma control test (ACT):[26] an instrument to evaluate asthma control, consisting of five items. The responses are defined on a five-point Likert-type scale. The instrument score ranges from five to 25 points. A score of five to 19 indicates no control and asthma control is between 20-25 points.[3]

Procedure. Once the project was approved by the Research Ethics Committee of INER, with code C47-18, patients were recruited in the waiting room of the Asthma Clinic. The instruments were answered individually, each participant was informed of the objectives of the research and was given instructions for answering the instruments, emphasizing their voluntary, anonymous and confidential participation, after signing the informed consent form.

Data analysis. The data were analyzed with SPSS version 24 and AMOS 25 for Windows. Descriptive statistics were used to summarize the characteristics of the participants and the study variables and the normality distribution of the data was evaluated with the Kolmogorov Smirnov-Lilliefors (KSL) statistic.

To demonstrate the reliability and validity of the instruments used, the measurement models of each scale were estimated through confirmatory factor analysis (CFA), taking as criteria the standardized regression weighting (factor loadings) and the following fit indices: the chi-square statistic (χ^2, $p > 0.05$), the resulting χ^2/gl ratio (< 3), the root mean square error of approximation (RMSEA < 0.08, 90% CI), the comparative fit index (CFI > 0.90) and the Tucker-Lewis index (TLI > 0.90). The internal reliability of the scales was examined using Cronbach's alpha coefficient (∝).

Subsequently, a preliminary Spearman's rho correlation analysis was performed for the apropos of deriving hypotheses based on the CSM and the subsequent construction of a pathway model (SEM). In this model, we attempted to corroborate that treatment perception mediate the effects between illness perception, adherence behaviors and asthma control.

This SEM model was tested using the maximum likelihood procedure with the Bootstrapping model and 95% corrected Bias (BC) with 1,000 samples, considering the fit indices χ^2, $p > 0.05$, χ^2/gl (< 3), RMSEA < 0.08, CI 90%, CFI > 0.90 and TLI > 0.90 and the direct, indirect and total effects.[27]

RESULTS

Descriptive. Most of the study participants lived in Mexico City (n = 187, 70%) and the State of Mexico (n = 61, 21.8%).

Table 1: Sociodemographic, clinical, and psychological data of the participants.

Variable	n (%), Mdn (IQR) or rank
Gender	
Women	198 (74.2)
Men	69 (25.8)
Age [years]	45 (23)
Residence	
México City	187 (70)
State of Mexico	61 (22.8)
Other*	19 (7.2)
Education	
Basic	108 (40.5)
High School	90 (33.7)
Professional	69 (25.8)
Occupation	
Professional/Labor	142 (53.2)
Home	84 (31.5)
No labor activity	41 (15.3)
Marital status	
Living with a partner	145 (54.4)
Single	70 (27.7)
Other	48 (17.9)
Evolution [months]	108 (192)
Illness perception questionnaire-revised	
Timeline chronic	15 (4), 5-20
Personal control	12 (2), 4-16
Coherence	8 (2), 3-12
Treatment control	9 (2),3-12
Beliefs about medicines questionnaire-specific	
Necessity	15 (5), 5-20
Concern	12 (5) 5-20
Necessity-concern differential	3 (6) -10–15
Medication adherence report scale-asthma	
Adherence	19 (5) 5-20
Adherent > 19	106 (39.7)
Non-adherent	161 (60.3)
Asthma control test	
Asthma control	20 (7) 5-25
Control ≥ 20	138 (51.6)
No control ≤ 19	129 (48.4)

The sample was not normally distributed on the variables of illness perception, treatment perception, adherence behaviors, and asthma control (KSL = 0.085-2.13, $p < 0.001$).
Mdn = median. IQR= Interquartile range.
* Oaxaca, Hidalgo, Morelos, Tlaxcala, Guanajuato, Querétaro, Guerrero and Veracruz.

Table 2: Global adjustment indicators of the measurement models.

Models	χ^2	gl	χ^2/gl	p	CFI	TLI	RMSEA	RMSEA CI 90% Low-high
IPQ-R (∝ = 0.73-0.87)	518.795	317	1.6	0.000	0.929	0.921	0.046	0.038-0.052
BMQ (∝ = 0.76-0.80)	143.791	87	1.6	0.001	0.967	0.961	0.050	0.044-0.076
MARS-A (∝ = 0.81)	7.790	4	1.9	0.100	0.986	0.965	0.073	0.000-0.149
ACT (∝ = 0.85)	6.972	5	1.3	0.223	0.996	0.993	0.039	0.000-0.100

CFI = comparative fit index. TLI = Tucker-Lewis index. RMSEA = root mean square error of approximation. IPQ-R = Illness perception questionnaire-revised. BMQ = beliefs about medicines questionnaire-specific. MARS-A = medication adherence report scale-asthma. ACT = asthma control test.

Table 3: Correlation analysis between IPQ-R, BMQ, MARS-A and ACT variables.

Instruments/variables		1	2	3	4	5	6	7	8
IPQ-R	1. Timeline chronic	—	—	—	—	—	—	—	—
	2. Personal Control	0.070	—	—	—	—	—	—	—
	3. Treatment Control	-0.026	0.383**	—	—	—	—	—	—
	4. Coherence	0.148*	0.240**	0.075	—	—	—	—	—
BMQ	5. Necessity	0.169**	0.114	0.191**	-0.010	—	—	—	—
	6. Concern	-0.012	-0.127*	-0.068	-0.429**	0.226**	—	—	—
	7. DNP	0.142*	0.177**	0.214**	0.344**	0.540**	-0.634**	—	—
MARS-A	8. Adherence	0.156*	0.048	-0.017	0.232**	0.193**	-0.242**	0.351**	—
ACT	9. Asthma Control	0.047	0.345**	0.149*	0.204**	-0.127*	-0.286**	0.125*	0.215**

IPQ-R = illness perception questionnaire-revised. BMQ = beliefs about medicines questionnaire-specific. MARS-A = medication adherence report scale-asthma. ACT = asthma control test. DNP = necessity-worry differential.
* $p \leq 0.05$. ** $p \leq 0.01$.

It was identified that in the illness perception (IPQ-R) high scores were obtained in temporality (chronic), treatment control, personal control and coherence.

Regarding the treatment perception (BMQ), patients reported a high need for treatment and a moderate concern for adverse effects due to the use of the control medication; this is evidenced by the positive score on the NPD. In the self-report of adherence behaviors to control treatment (MARS-A), high scores were obtained in this variable, that is, they self-reported high levels of adherence, and in asthma control (ACT) it was identified that more than 51% were controlled, but only 10.9% (n = 29) qualified for total control of the disease. *Table 1* describes in detail the variables studied in the participants.

Measurement models. *Table 2* shows the reliability analyses and goodness-of-fit indices of the measurement models for each of the instruments used. The results show that each instrument has reliability indices ranging from acceptable to very good (∝ 0.73 to 0.85), while the data for the CFI and TLI indicators show an excellent fit based on the criteria considered (CFI > 0.90; TLI > 0.90). Only in the RMSEA result, the MARS-A scale and the ACT exceed the criterion of 0.08 for the range in the confidence interval. These findings show that the instruments used have acceptable evidence of reliability and validity.

Correlation analysis. *Table 3* shows the correlations between each of the variables evaluated for the subsequent construction of the SEM model. Although the correlation data range from weak to moderate, the most relevant would be the relationships between: 1) personal control, coherence (IPQ-R) and asthma control; 2) coherence, temporality (IPQ-R) and need for treatment (DNP); 3) need for treatment (DNP) and adherence behaviors; and 4) the weak correlations between personal control and treatment control (IPQ-R) and adherence behaviors.

Mediation model. *Figure 1* shows the simplified mediation model in which it is observed that illness perception (personal control and treatment control) has significant effects in explaining asthma control ($\beta = 0.55$, $p < 0.05$), but not in explaining adherence behaviors

(β = 0.00, p > 0.05), in the same sense, timeline chronic and coherence about the disease do not contribute in disease control (β = 0.00, p > 0.05) nor in adherence behaviors (β = 0.13, p > 0.05), at least directly.

Similar results are observed when analyzing the effects of treatment perception on asthma control (β = 0.01, p > 0.05).

Now, by including treatment perception as a mediating variable, considerable effects can be observed between illness and treatment perception (β = 0.48, p < 0.05), adherence behaviors (β = 0.25, p < 0.05) and asthma control (β = 0.28, p < 0.05).

When analyzing the statistically significant paths in the model in *Figure 1*, it can be seen that the relationship between illness perception and adherence behaviors is mediated by treatment perception (β = 121, CI = 0.006, 0.341). In contrast, illness perception generates significant effects on asthma control (β = 0.55, p < 0.05), independently of the mediating effect of treatment perception *(Table 4)*.

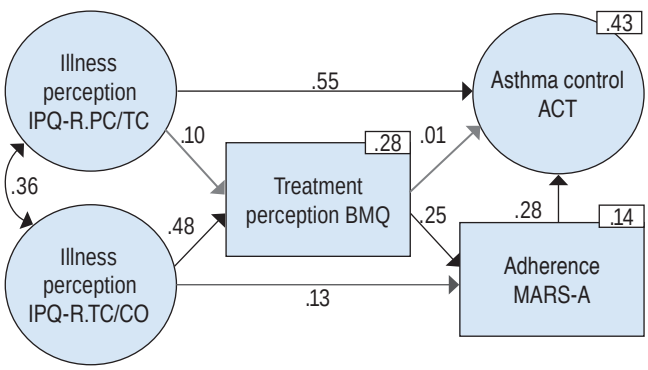

Figure 1: Simplified mediation model. Standardized path coefficients between model variables to explain asthma control are shown. Black lines represent statistically significant effects (p < 0.05) and gray lines represent non-statistically significant effects (p > 0.05). IPQ-R.PC/TC: two of the illness perception variables were grouped: personal control and treatment control. IPQ-R.TC/CO: two of the illness perception variables were grouped together: timeline chronic and coherence. BMQ: was calculated with the difference between the score obtained between necessity and concern, a variable previously defined as NCD.

The findings of the model translate into the fact that the illness perception explains 28% of the variance of the treatment perception (R2 = 0.28), together, these variables only explain 14% of the variance of adherence behaviors (R2 = 0.14) and the model, as a whole, manages to explain 43% of the variance of asthma control (R2 = 0.43). Finally, regarding the statistical fit of the model, it is identified as having acceptable indicators (χ^2 = 34.615, p = 0.002, gl = 14, χ^2/gl = 2.4, CFI = 0.937, TLI = 0.874 and RMSEA = 0.074 [CI at 90% = 0.043-0.106]).

DISCUSSION

Given that a significant proportion of patients with asthma are not adherent to their treatment (75%) and that more than 50% have difficulties in controlling their disease,[2,3] it is necessary to identify the variables that cause these problems to persist, as well as to determine the variables that need to be modified in order to address them. It is in this sense that the findings of the present study become relevant by showing an explanatory route to address the problems of adherence to treatment and asthma control, considering the effects of psychological variables such as beliefs about the disease and the treatment.

The initial results show a profile of patients with a positive illness perception (perception of asthma as a chronic disease, perceived ability to control the disease, positive attitude regarding the effects of treatment and a clear understanding of asthma) and of the treatment (greater perception of the need for treatment and less concern about its adverse effects). Similar evidence has been found from different parts of the world, including Mexico, mainly when relating these variables to the level of adherence[4,8,9,28] and asthma control.[29,30]

In relation to adherence behaviors, patients showed high scores on this variable, i.e., infrequent self-reporting of behaviors such as not using treatment, changing the number of puffs, or voluntary adjustments in the timing of treatment. However, more than 60% of the participants were categorized as non-adherent. These results are

Table 4: Total, indirect and direct effects of the multiple mediation model.

	Results				
	BMQ	MARS-A $_{(De-Te)}$	ACT $_{(De-Te)}$	MARS-A $_{(Ie\ x\ BMQ)}$	ACT $_{(Ie\ x\ BMQ)}$
Predictors	β	β	β	β (CI 95%)	β (CI 95%)
IPQ-R. PC/TC	0.101	0.000, 0.025	0.553, 0.561	0.025 (-0.165, 0.123)	0.008 (-0.021, 0.065)
IPQ-R. TC/CO	0.483	0.171, 0.292	0.000, 0.084	0.121 (0.006, 0.341)	0.084 (-0.011, 0.319)

BMQ = beliefs about medicines questionnaire-specific. MARS-A = medication adherence report scale-asthma. ACT = asthma control test. IPQ-R = illness perception questionnaire-revised. De = direct effects. Te = total effects. Ie = indirect effects. CI = confidence interval. IPQ-R. PC/TC = personal control and treatment control. IPQ-R. TC/CO = timeline chronic and coherence.

consistent with findings in African-American, Caucasian and Spanish-speaking asthma populations in the United States and patients in Mexico.[25,31-33] In that case, it should not be overlooked that sometimes socially valued behaviors such as adherence are often overestimated.[34,35]

However, it would seem contradictory to have a positive illness perception and the treatment, to report a high level of adherence and that nearly 50% of the patients did not have adequate control of the disease. In this aspect, it would be necessary to consider that the lack of asthma control is also linked to factors such as comorbidities (allergies, other respiratory diseases, obesity), exposure to triggers (pollution, smoke from various substances) and negative psychosocial aspects (depression, anxiety, economic difficulties and a negative illness perception).[2,3,30]

As mentioned above, the proposed model suggests sequential work to modify/improve illness perception, treatment perception, adherence behaviors and asthma control. Although the percentage of variance explained in adherence is low (14%), it is important to highlight that overall the model explains 43% of the variance in asthma control.

This is because addressing adherence and control problems would have a positive impact on the frequency of emergency care and hospitalization for asthma attacks, economic repercussions, emotional problems, poor quality of life and death.[2,3,36]

In contrast to the proposed model, other studies such as that of Horne and Weinman[22] developed a model to explain adherence behaviors (R2 = 0.26), but including the observed variables of timeline chronic, consequences (CSM), and necessity and concern (NCF). In turn, Chapman *et al.*[19] developed a model where only the NCF variables were considered, which showed very weak and negative effects of positive treatment perception on adherence (r = -0.08) and better for explaining asthma control (r = 0.25). Finally, Kosse *et al.*[1] proposed a correlational model shown as path analysis, where the relationships between illness perception (coherence, temporality and treatment control) and treatment (DNP), adherence behaviors and asthma control range from r = 0.13 to 0.38.

CONCLUSIONS

The proposed model suggests that multidisciplinary interventions can be developed that focus on favoring an adequate understanding of the disease and treatment, a perception of asthma as a chronic disease, increasing the perceived ability to manage the disease and the need to use the treatment, as well as minimizing the concern for the adverse effects of the control treatment. All of this is aimed at using treatment consistently over time, using it at an adequate frequency and dose, and avoiding conditional use of treatment (only when symptoms are present), in order to improve disease control.[2,3,37,38]

One of the limitations of the study is the low explanatory level of the model for adherence behaviors (R2 = 0.14), since a better performance was expected. However, this opens up new proposals for exploring other variables related to adherence, such as the experience of adverse effects, satisfaction with the medication or economic problems,[39] as well as including the perception of the need for treatment in asymptomatic periods.[40]

In relation to asthma control, the use of self-report methods is a limitation; for future studies it would be advisable to include exacerbations, pulmonary function and risk variables for poor asthma control in this evaluation.[3] Finally, another limitation could be oriented towards the characterization of the sample, where more than 74% of the participants were women. Although no process was carried out to have a proportionate sample, this type of variation is expected because the prevalence of asthma is higher in women than in men during adolescence and adulthood, contrary to what occurs in childhood.[2,3]

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Clinical and chest imaging characteristic in patients with COVID-19 in a hospital from Tegucigalpa, Honduras

Características clínicas y de imagen de tórax en pacientes con COVID-19 en un hospital de Tegucigalpa, Honduras

Sandra Cárcamo,* Walter Pacheco,[‡,§] Glenda Ortiz,[§,*] María Félix Rivera*

*Universidad Nacional Autónoma de Honduras; [‡]Hospital María de Especialidades Pediátricas; [§]Instituto Hondureño de Seguridad Social.

ABSTRACT. Introduction: the role of imaging resources for the characterization of the spectrum of radiological manifestations, through standardized language and structured reports, serves as a guide for treatment and therapy in COVID-19 patients. **Purpose:** to determine the clinical-imaging characteristics in the chest tomography in patients with COVID-19 at the Hospital María de Especialidades Pediátricas. **Material and methods:** observational, cross-sectional study, with an analytical component, carried out at the Hospital María de Especialidades Pediátricas, April 2020-April 2021. All data were obtained from clinical records and digital image archive, 149 patients met the case definition. The inclusion criteria were: confirmed or probable COVID-19 patients 18 years or older who were hospitalized and underwent RT-PCR or antigen tests and HRCT. On the other hand, three scales were used to objectify affectation, severity and degree of suspicion for the prediction of COVID-19 by computerized tomography (CT). **Results:** the most affected population where female, the most frequent age range was between 40-59 years, (mean of 56) with comorbidities such as hypertension, obesity and diabetes or prediabetes. Most of the patients presented in a chronic or advanced phase of the disease, the following patterns where found the most frequently; cobblestone (80.5%), pleuroparenchymal bands (79.5%) and ground glass pattern (73.8%). There is a strong correlation between the predominant pulmonary patterns and the tomographic evolution phase (Pearson's correlation coefficient 0.65). **Conclusion:** computerized tomography is a very valuable tool for diagnosing COVID-19 infection, both in the initial assessment of lung involvement and for its follow-up.

Keywords: COVID-19, chest tomography, pulmonary patterns, CORADS RSNA.

RESUMEN. Introducción: el papel de los recursos de imagen para la caracterización del espectro de manifestaciones radiológicas mediante un lenguaje estandarizado e informes estructurados sirve de guía para el tratamiento y terapia en pacientes COVID-19. **Propósito:** determinar las características clínicas imagenológicas en la tomografía de tórax en pacientes con COVID-19, Hospital María de Especialidades Pediátricas. **Material y métodos:** estudio observacional, transversal, con componente analítico, realizado en el Hospital María de Especialidades Pediátricas de abril de 2020 a abril de 2021.Todos los datos fueron obtenidos de expedientes clínicos y archivo digital de imágenes, 149 pacientes cumplían con la definición de caso. Los criterios de inclusión fueron: pacientes confirmados o probables por COVID-19 mayores de 18 años que fueron hospitalizados, a quienes se les realizó prueba PCR-RT o antígenos y tomografía de tórax AR. Se utilizaron tres escalas para objetivar afectación severidad y grado de sospecha para predicción de COVID-19 por tomografía computarizada (TC). **Resultados:** los más afectadas fueron del sexo femenino, rango de edad más frecuente fue entre 40-59 años, (media de 56), con comorbilidades como hipertensión, obesidad y diabetes/prediabetes. La mayoría de los pacientes se presentaron en una fase crónica/avanzada de la enfermedad, encontrando con mayor frecuencia los siguientes patrones: empedrado (80.5%), bandas pleuroparenquimales (79.5%) y patrón en vidrio deslustrado (73.8%). Existe una correlación fuerte entre los patrones pulmonares predominantes y fase de evolución tomográfica (coeficiente de correlación de Pearson 0.65). **Conclusión:** la TC de tórax es útil para diagnosticar la infección por COVID-19 tanto en la valoración inicial de la afectación pulmonar y seguimiento.

Palabras clave: COVID-19, tomografía de tórax, patrones pulmonares, CORADS RSNA.

Correspondence:
Sandra Cárcamo, MD
Universidad Nacional Autónoma de Honduras.
E-mail: sandriscarcamo87@gmail.com

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INTRODUCTION

The pandemic generated by the new coronavirus (COVID-19) since its initial emergence in late December 2019 in Wuhan City, China, has left 5.65 million deaths worldwide.[1]

The Hospital María de Especialidades Pediátricas is a national referral hospital that provides care for children under 18 years of age; however, due to the global

emergency it joined the national hospital network for the care of patients with COVID-19. The World Health Organization (WHO) has a definition of a COVID-19 case, according to clinical manifestations and laboratory tests, suggested as follows: «confirmed case» person with reverse transcriptase polymerase chain reaction-reverse transcriptase (RT-PCR) test result positive for COVID-19, independent of signs and symptoms; «suspected case» patient with acute respiratory illness (fever and at least one symptom or sign of respiratory illness such as cough or dyspnea) and history of travel or residence in localities with reported community transmission during the 14 days prior to the onset of signs and symptoms. Also probable case: a suspected patient whose PCR-RT result is inconclusive or a suspected patient for whom laboratory testing could not be performed for any reason. In Honduras, the Ministry of Health approved the use of the antigen test for confirmation of COVID-19 according to the recommendations of the Pan American Health Organization (PAHO) and the Center for Communicable Diseases (CDC).[2,3]

This infection can present as mild, moderate or severe disease, including severe pneumonia, acute respiratory distress syndrome (ARDS), sepsis and septic shock, even leading to death.[4]

Computed tomography (CT) is considered the routine modality for the diagnosis, management and follow-up care of patients with COVID-19 pneumonia. It can aid in the early detection of pulmonary abnormalities for screening patients with suspected disease, especially patients with an initial negative RT-PCR screening result.[5-7]

By means of universal scales such as the Total Severity Score (TSS) and the Pulmonary Tomographic Assessment Tomographic Assessment Pulmonary Score System adapted to segmental involvement (PATPAS), a scale applied at the national level with which it is possible to know what percentage of the lung is affected by tomography.

The apropos of the study was to determine the clinical imaging features on chest CT in adult patients with COVID-19 at Hospital Maria de Especialidades Pediátricas, from April 2020 to April 2021.

MATERIAL AND METHODS

Observational, cross-sectional study, with analytical component, conducted at the Hospital María de Especialidades Pediátricas from April 2020 to April 2021 located in the city of Tegucigalpa. There was a total population of 1,730 hospitalized patients, of which only 461 underwent institutional tomography, the sample was 149 patients who met the case definition.

Inclusion criteria were confirmed or probable COVID-19 patients older than 18 years who were hospitalized and underwent PCR-RT or antigen testing and high-resolution (HR) chest CT on the GE ligthspeed 64-slice facility CT scanner.

Procedure

The files of radiological studies and clinical records of patients admitted with a confirmed or probable diagnosis of COVID-19 who underwent tomography were reviewed, taking into account only those patients who presented tomographic findings typical of COVID-19, and then reevaluated together with the radiologist with four years of experience.

The findings were classified as follows: central (predominantly in the inner two thirds of the lung), peripheral (predominantly in the outer third of the lung) central and peripheral (in multiple lung segments) according to the European Society of Radiology and patchy distribution was added.[8]

To measure the degree of lung involvement by CT, the TSS was used, estimating the percentage of involvement in each lobe by the following score: 0 (none), 1 (affecting less than 5% of the lobe), 2 (affecting 5-25% of the lobe), 3 (affecting 26-49% of the lobe), 4 (affecting 50-75% of the lobe) or 5 (affecting more than 75% of the lobe). The CT score was obtained by summing the scores of the five lobes, for each patient the CT score was in the range of 0 to 25.[9]

In addition, two scales were applied to estimate the severity and suspicion of COVID-19: PATPAS of the Honduran Association of Radiology and Imaging (AHRI), and the Reporting and Data System for COVID-19 (CO-RADS) of the Radiological Society of North America (RSNA), respectively.[10]

PATPAS system: a five-point score was applied for each lung segment (0% no involvement, 25% mild, 25-50% moderate, 50-75% severe and more than 75% severe). CO-RADS provides a standardized system and evaluation scheme that simplifies reporting with a five-point scale of suspicion for lung involvement by COVID-19 on chest CT. CO-RADS 0: scans that are incomplete or of insufficient quality. CO-RADS 1: very low level of suspicion of lung involvement. CO-RADS 2: low level of suspicion of pulmonary involvement. CO-RADS 3: indeterminate findings of pulmonary involvement. CO-RADS 4: high level of suspicion of lung involvement by COVID-19 based on CT findings that are typical. CO-RADS 5: implies a very high level of suspicion of lung involvement based on typical CT findings. CO-RADS 6: was introduced to indicate COVID-19 proven by a positive RT-PCR test.[11,12]

Statistical analysis: univariate statistical analysis was performed (for qualitative variables; frequencies, proportions, 95% confidence intervals) and quantitative variables; means, mode, median, standard deviation. For bivariate analysis, Pearson correlation tests were used to

see if the differences were statistically significant between the predominant pattern - evolutionary phase and the predominant pattern - disease severity variables.

The statistical programs used were SPSS, EPI INFO 7.2 and Excel for Windows.

RESULTS

We evaluated 149 patients (77 women) with the most frequent age range between 40-59 years of COVID-19 patients, with a mean of 56 years. The most frequently found antecedents were hypertension (69 [46.3%]), obesity (49 [32.9%]) and diabetes/prediabetes (23 [15.4%]). Clinical manifestations at admission were dyspnea (132 [93.3%]), fever/febrile (124 [83.2%]) and cough (109 [73.2%]) *(Table 1)*.

Patients were hospitalized between a most frequent range of one to seven days with a mean interval of 1.5 (0.643 standard deviation), of which 28 (18.8%) were admitted to ICU (intensive care unit), deceased patients were 17 [11.4%].

During the tomographic evaluation, the most frequent pulmonary patterns were: cobblestone pattern (120 [80.5%]), pleuroparenchymal bands (118 [79.2%]) and ground glass pattern (110 [73.8%]), reticular pattern (82 [55%]), and in lower percentage vascular dilatation (56 [37.6%]) and consolidated pattern (52 [34.9%]) *(Figures 1 to 4)*.

Regarding the phases found, the resorption phase was observed most frequently (69 [46.3%]) followed by the peak phase (40 [26.8%]) *(Table 2)*.

Each patient was found to have five of five lung lobes affected, 144 (96.6%), with a total percentage of involvement of 26-49%, (96 [62.4%]); the most characteristic distribution of lung involvement was central and peripheral (86 [57.7%]), and without segment predominance (86/57.7%) followed by localization in posterior segments (59/39.6%), all with statistical significance ($p < 0.05$). The PATPAS severity score presented by the patients was moderate (93 of 149 patients [62.4%]).

Eighty-six patients were identified with positive laboratory tests by PCR-RT, which were included within the CORADS 6 category (cases already confirmed by laboratory plus typical finding by CT), in addition patients confirmed by antigen test were included, thus adding up to a total of 143 out of 149 (93%); only six patients had a negative laboratory test by PCR-RT and antigen, which were categorized as CO-RADS 5 with very high suspicion of presenting the disease by typical findings by CT AR ($p < 0.05$).

The Pearson correlation (0.65) obtained with a null probability (0%) of being random allows us to conclude that there is a high positive correlation between the predominant pulmonary patterns and the phase of tomographic evolution.

Table 1: Epidemiological-clinical characteristics in patients with COVID-19. N = 149.

General data	n (%)	p (χ^2)
Gender		
Female	77 (51.7)	0.000
Male	72 (48.3)	
Median age 56 years		0.000*
20-39	25 (16.8)	
40-59	64 (43.0)	
60-79	47 (31.5)	
80 years and more	13 (8.7)	
Procedence		
Tegucigalpa, Francisco Morazán	149 (100.0)	
Pathological antecedents		
Hypertension	69 (46.3)	0.066
Obesity	49 (32.9)	0.514
Diabetes mellitus/prediabetes	23 (15.4)	
Heart disease	11 (7.4)	0.145
Asthma	10 (6.7)	0.559
Alcoholism and smoking	7 (4.7)	0.034
Neoplasia	2 (1.3)	0.388
COPD	2 (1.3)	0.388
Nephropathy	1 (.7)	0.624
Other antecedents		
Hypothyroidism	11 (7.4)	0.004
Clinical manifestations		
Dyspnea	139 (93.3)	0.441
Febrile fever	124 (83.2)	0.306
Cough	109 (73.2)	0.427
Myalgia	36 (24.2)	0.059
Headache	33 (22.1)	0.196
Arthralgia	31 (20.8)	0.118
Anosmia	25 (16.8)	0.476
Ageusia	22 (14.8)	0.276
Odynophagia	22 (14.8)	0.063
Other symptoms		
Diarrhea	17 (11.4)	0.000
Rhinorrhea	19 (12.8)	0.000

* Values obtained for Student's t.
Source: data obtained from the archive of the Hospital María de Especialidades Pediátricas

DISCUSSION

A study conducted in Colombia by Marrin Sanchez stated that this disease occurs more frequently in the male sex at a mean age of 65.75 ± 18.1. In this study the female sex was more frequent and the age ranged between 40-59 years of age with a mean of 56 years. However, a study carried out by PAHO states that the incidence between 40-59 years of age is equal in both sexes, and as age increases, it is more frequent in men.[13,14]

The most frequently found personal pathologic antecedents were hypertension, obesity and diabetes/

prediabetes (similar to the study by Peña *et al.* where hypertension ranked first), as well as that presented by Murrieta *et al.* where patients showed to have two or more comorbidities.[15,16]

In our study, the initial clinical manifestations that prevailed were dyspnea (132 [93.3%]), fever/febrile fever (124 [83.2%]) and cough (109 [73.2%]), a finding similar to that of Song *et al.* observing fever (49 of 51, 96%) and cough (24 of 51, 47%) among the most frequent symptoms, as well as a retrospective study in patients hospitalized in the ICU, where they reported that the most common initial symptoms were fever (92%), cough (68%) and dyspnea (49%).[17,18]

It is noteworthy that most of the patients in this research presented in a chronic/advanced phase of the disease, finding as predominant patterns the cobblestone (120/149; 80.5%), pleuroparenchymal bands (118/149; 79.5%) and in third place ground-glass pattern (110/149; 73. 8%), without identifying any case with findings of atoll, pneumothorax or twinning tree, other studies do report ground glass opacities as the predominant finding followed by the consolidation

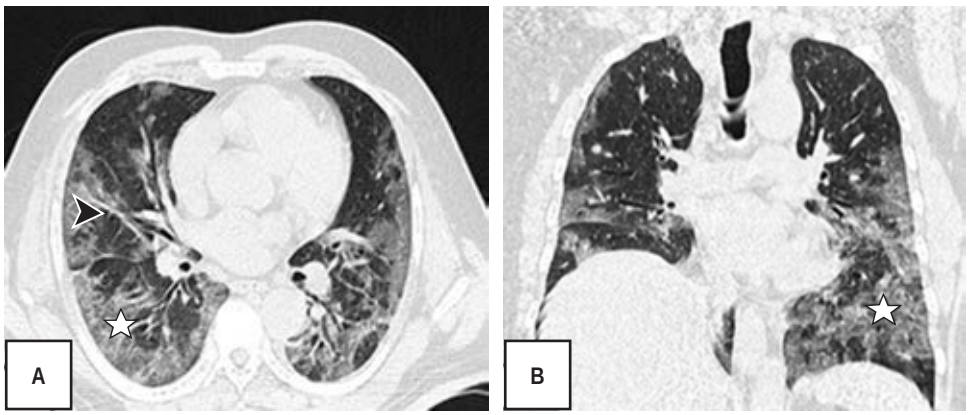

Figure 1:

A-B) Shows cobblestone pattern (star) characterized by areas of thickening of interlobular septa with areas of ground glass distributed bilaterally and peripherally, associated vascular dilatation (arrowhead).

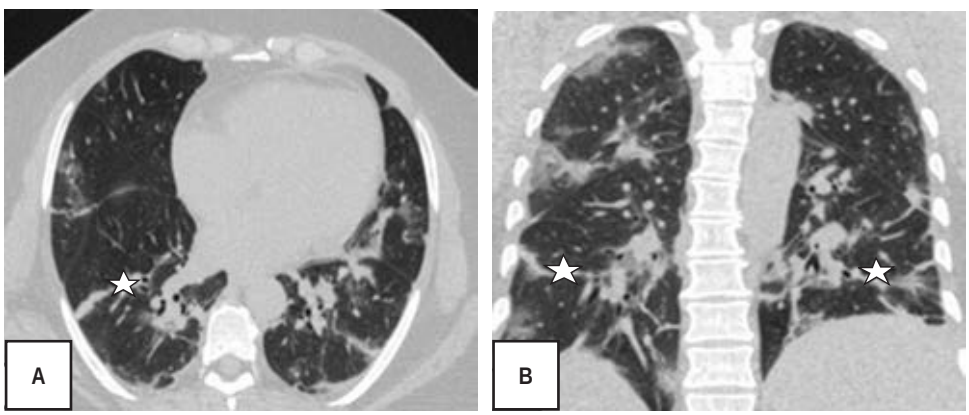

Figure 2:

A-B) Bilateral pleuroparenchymal bands are identified (star) with scanty areas in depulidized glass distributed centrally and peripherally predominantly in the posterior basal segments.

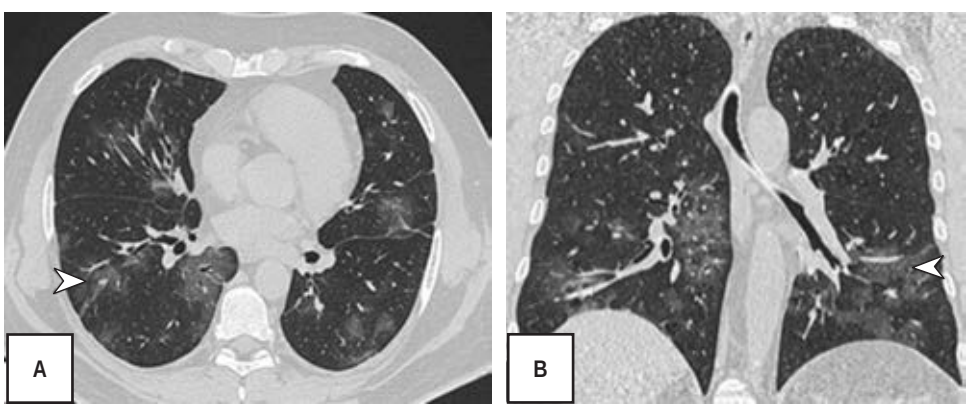

Figure 3:

(A-B) Showing ground glass opacities with patchy distribution in both lung fields (arrowhead).

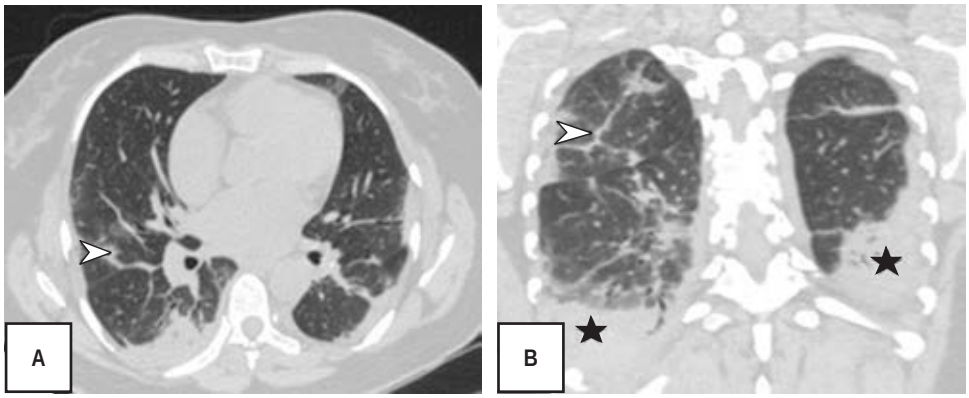

Figure 4:

A-B) Shows peripheral pulmonary consolidation (star) predominating in the lung bases with air bronchogram inside and pleuroparenchymal bands protruding in the uppermost segments (arrowhead).

Table 2: Lung patterns by AR tomography in patients with COVID-19. N = 149.

Tomographic patterns	n (%)	χ^2	p
Tarnished glass pattern	110 (73.8)	0.017	0.521
Consolidated pattern	52 (34.9)	1.581	0.140
Cobblestone pattern	120 (80.5)	0.221	0.395
Reticular pattern	82 (55.0)	1.170	0.181
Pleuroparenchymal bands	118 (79.2)	0.958	0.219
Bronchial thickening	10 (6.7)	0.263	0.441
Vascular dilatation	56 (37.6)	4.460	0.025
Pleural effusion	10 (6.7)	1.413	0.200
Adenopathies	10 (6.7)	3.477	0.057
Atelectasis	44 (29.5)	0.294	0.359
Others (granuloma)	22 (14.7)	15.549	0.000
CT disease stage			
Initial	11 (7.4)	7.152	0.004
Progressive	29 (19.4)	21.682	0.000
Peak	40 (26.9)	32.925	0.000
Resorption	69 (46.3)	77.384	0.000

CT = computed tomography. HR = high resolution.
Source: data obtained from the archive of the Hospital María de Especialidades Pediátricas.

pattern and in this regard pleural effusion, pericardial effusion, lymphadenopathy, cavitation, the reverse halo or atoll sign and pneumothorax are rare, but can be observed with the progression of the disease.[19-21]

Segmental involvement was without predominance and with a central and peripheral distribution in equal percentage with 57.7%, different to that published by Pan F *et al.*, where the lower lobes were more likely to be involved and in general, the subpleural distribution of lesions was more frequent than central lung lesions.[22]

Soriano *et al.* reported that the presence of ground-glass opacities, reticular pattern, cobblestone pattern, subpleural lines, pleural thickening and fibrosis were more frequently found in the intermediate/progressive phase, especially in the advanced phase; similarly we observed a significant correlation (Pearson's index of 0.65) between the predominant pattern and the progressive phase of the disease.[23] The CT scores of the progressive stage group were significantly higher than those of the early stage group; however, in this study there was no statistical significance between CT pattern and severity score.

CONCLUSIONS

Recognizing the evolutionary phases of COVID-19 disease will help us to provide adequate follow-up and to know the patient's prognosis, for which the chest tomography complemented with the PCR-RT laboratory test is the diagnostic basis when undertaking the management.

The Hospital María de Especialidades Pediátricas as a national reference hospital during the pandemic did a great job, assisting adults with COVID-19 in the face of a national problem, thus obtaining complete and valuable information for the present study.

The study was limited in some deceased patients because the laboratory test was not presented in the file, since it was necessary even if it was negative or positive.

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Descending necrotizing mediastinitis. A 16-year experience in a referral center

Mediastinitis necrosante descendente. Experiencia de un centro de referencia durante 16 años

Luis Iván Waldo-Hernández,* José Pablo Rueda-Villalpando,* Marco Antonio Cruz-López,* Juan Carlos Vázquez-Minero*

*Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico City, Mexico.

ABSTRACT. Introduction: descending necrotizing mediastinitis (DNM) refers to mediastinal infections originating in the oropharyngeal and cervicofacial region that spread through the deep planes of the cervical fascia into the mediastinum. Multiple organ failure and high mortality are related to the delay in diagnosis and medical-surgical treatment. Surgical treatment remains controversial, with supports ranging from isolated cervical drainage to cervical drainage and thoracotomy and/or median sternotomy. **Objective:** to know the morbidity and mortality related to the surgical management of NDM as well as the main etiology prevalent in our environment. **Material and methods:** it is a retrospective study in a period between 2006 and 2022 of patients with MND who were hospitalized and surgically treated in the Thoracic Surgery Service of the National Institute of Respiratory Diseases Ismael Cosío Villegas. **Results:** 51 patients were included, 38 men, age 39.19 ± 14.06 years. 41 patients were classified ENDO IIB, 9 ENDO I, the main cause was odontogenic in 28 patients. Days of hospital stay of 22.65 ± 15.61 days. 12 patients operated by cervicotomy and 39 patients combined approach. 22 patients required reintervention. 14 deaths, the most prevalent cause of septic shock. **Conclusions:** the approaches used according to the availability of resources over time and hospital stay and mortality do not differ from what is reported in the literature.

Keywords: mediastinitis, abscess, sternotomy, cervicotomy, thoracoscopy.

RESUMEN. Introducción: la mediastinitis necrosante descendente se refiere a las infecciones mediastínicas que se originan en la región orofaríngea y cervicofacial que se diseminan a través de los planos profundos de las fascias cervicales hacia el mediastino. La falla orgánica múltiple y la alta mortalidad están relacionadas con el retraso en el diagnóstico y tratamiento médico-quirúrgico. El tratamiento quirúrgico sigue siendo controvertido, con soportes que van desde el drenaje cervical aislado hasta el drenaje cervical y la toracotomía y/o esternotomía media. **Objetivo:** conocer la morbimortalidad relacionada con el manejo quirúrgico de la mediastinitis necrosante descendente, así como la principal etiología prevalente en nuestro medio. **Material y métodos:** es un estudio retrospectivo en un período comprendido entre 2006 y 2022 de pacientes con mediastinitis necrosante descendente que fueron hospitalizados y tratados quirúrgicamente en el Servicio de Cirugía Torácica del Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. **Resultados:** se incluyeron 51 pacientes, 38 hombres, edad de 39.19 ± 14.06 años; 41 pacientes se clasificaron como ENDO IIB, nueve ENDO I, la causa principal fue odontogénica en 28 pacientes. Días de estancia hospitalaria de 22.65 ± 15.61 días. Operados por cervicotomía 12 pacientes y abordaje combinado 39 pacientes. 22 pacientes requirieron reintervención quirúrgica. Hubo 14 defunciones, la causa más prevalente fue choque séptico. **Conclusiones:** los resultados no difieren de los reportados en la literatura, en cuanto al tipo de abordaje de acuerdo con la disponibilidad de los recursos con el paso del tiempo, la estancia hospitalaria y mortalidad.

Palabras clave: mediastinitis, absceso, esternotomía, cervicotomía, toracoscopia.

Correspondence:
Luis Iván Waldo-Hernández, M.D.
Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico City, Mexico.
E-mail: ivanwaldo2303@hotmail.com

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INTRODUCTION

Mediastinitis is a severe infection that affects the connective tissue that fills the mediastinum and surrounds the median thoracic organs;[1] it is a harsh medical condition of infectious origin. Descending necrotizing mediastinitis (DNM) refers to mediastinal infections originating in the oropharyngeal and cervicofacial regions that spread through the deep planes of the cervical fascia into the mediastinum, causing cellulitis, necrosis, abscesses, and sepsis.[2,3] DNM refers to an infection

that begins in the oropharyngeal or cervical region, then spreads through the fascial planes in the mediastinum and may or may not spread to the pleural cavity.[3-6] Its evolution is rapidly progressive towards tissue necrosis, with high mortality levels (40%) due to sepsis and multiple organ failure without timely and appropriate treatment.[4] Surgical treatment plays an essential part in this disease's clinical evolution and prognosis. This study aims to determine the postoperative morbidity and mortality in treatment for DNM, as well as the most prevalent approaches and etiologies in our environment.

MATERIAL AND METHODS

This is a retrospective analytical study, conducted in a period from 2006 to 2022, that included all patients diagnosed with DNM treated surgically at the Ismael Cosío Villegas National Institute of Respiratory Diseases (INER) in Mexico City, registered in the database of such procedures of the sub-directorate of surgery. Clinical records were reviewed, including epidemiological data, imaging studies, and available cultures. All patients included were diagnosed based on the criteria of Estrera *et al.*[7] The diagnoses were corroborated by computed tomography and were evaluated based on the classification of Endo *et al.*[8] Patients were excluded when they presented with mediastinitis due to other causes, such as those secondary to esophageal or tracheal perforation secondary to trauma, post-surgical mediastinitis, or those with a diagnosis other than DNM such as superficial or deep neck abscess. Likewise, patients were excluded when retrieving their complete physical or electronic files was impossible.

RESULTS

A total of 51 patients were included, 13 women (25.49%) and 38 men (74.51%); the mean age was 39.19 ± 14.06 years; 13 of them (25.49%) had some comorbidity, the most prevalent being diabetes mellitus and systemic arterial hypertension; 41 patients (80.39%) were classified by tomography as ENDO IIB, nine (17.64%) as ENDO I and one (1.97%) as ENDO IIA. The leading cause and origin of DNM was odontogenic in 28 patients (54.9%), followed by a peritonsillar abscess in 22 patients (43.13%). The average number of days of hospital stay was 22.65 ± 15.61 days. A total of 12 patients (23.52%) underwent surgery by cervicotomy and 39 those (76.48%) with a combined approach, with cervicotomy + median sternotomy being the most common approach in 21 patients (41.17%), followed by cervicotomy + thoracotomy in 16 patients (31.37%). A total of 22 patients (43.13%) needed some surgical reintervention, the most frequent cause being negative pressure therapy replacement in the 11 patients (21.56%) in which it was used, with a mean of 10.78 ± 10.01 days of negative pressure therapy. There were 14 deaths (27.45%); the most common cause was septic shock. The isolated pathogens were multimicrobial, the most common being *Klebsiella pneumoniae*, streptococcus, *E. coli*, *Serratia marcescens*, and *Candida*. Post-surgical complications occurred in nine patients (17.64%), pulmonary thromboembolism in two patients (3.92%), acute myocardial infarction, acute renal failure, upper gastrointestinal bleeding, supraventricular tachycardia, sternal osteomyelitis, and right cord palsy in one patient, each (1.96%).

DISCUSSION

DNM is a condition originating in a dental or oropharyngeal infection with a rapidly progressive course that can lead to sepsis and often to death. The cause of DNM is distributed as odontogenic (36-47%), pharyngeal or tonsillar (33-45%), cervical (15%), and other head and neck infections (5%).[1,4] In our series, the odontogenic origin was the most frequent, with 54.9% of the cases, followed by a peritonsillar abscess.

The most common bacterial flora is an aerobic and anaerobic mix, with β-hemolytic streptococcus being the most commonly isolated.[2] Cultures in our series were negative in most cases; however, it was possible to isolate *Klebsiella pneumoniae*, *Streptococcus*, *E. coli*, *Serratia marcescens*, and *Candida*, in some cases.

Pearse described the anatomical routes of DNM dissemination in 1983; he was the first to identify this group of patients, which he called «secondary to cervical suppuration».[5] The dissemination routes from the neck to the mediastinum are through the pretracheal, paraesophageal, prevertebral, and retropharyngeal spaces, and along the carotid sheath. The main space considered «dangerous» is the retropharyngeal space extending from the skull's base to the mediastinum. This entity's infectious, multimicrobial, predominantly anaerobic nature, association with other comorbidities, and negative intrathoracic pressure ease its spread.[9-11]

Imaging studies' role is vital in diagnosis, without neglecting a thorough clinical history and physical examination. The main findings in the plain chest x-ray raise the suspicion of DNM and the clinical signs and symptoms of severe infection associated with a history of cervical, dental, or oropharyngeal infection. Said radiological findings can be widening of the mediastinum, pneumomediastinum, mediastinal hydro-aerial levels, anterior displacement of the tracheal air column due to a prevertebral opacity of the soft tissues, enlargement of the cardiac silhouette and loss of the normal lordosis of the cervical spine, as well as unilateral or bilateral pleural effusion.[9,10,12] Cervicothoracic computed tomography (CT) should be performed immediately, as

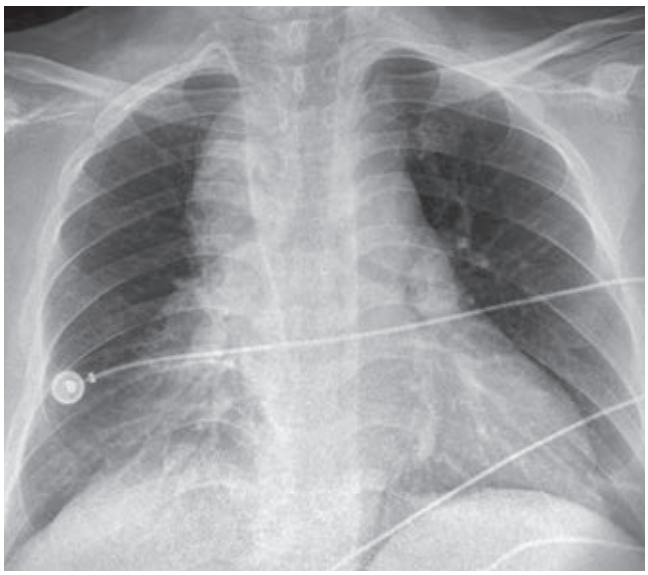

Figure 1: Representative initial chest radiography with mediastinal widening.

CT of the chest and neck can reveal detailed information regarding the extent of the necrosis process and suggests, within the framework of the surgical treatment approach, the best tactic for effective drainage to optimize the best post-surgical outcome for the patient and with it the need for fewer reinterventions.[9,10,13-17]

In our series, chest radiography continues to be the initial study in all patients with respiratory problems due to its accessibility and quick results *(Figure 1)*; however, chest tomography continues to be the gold standard at our institution for the diagnosis and planning of surgical management in those with mediastinitis *(Figure 2)*.

Management via surgery, and particularly a superior form of mediastinal drainage, is still controversial and ranges from cervical drainage by cervicotomy to a combination of cervical drainage and a thoracic approach using mediastinoscopy, thoracoscopy, thoracotomy, median sternotomy, or a Clamshell incision.[1,12] At present, mediastinal and cervical drainage have been particularly benefited with the emergence of negative pressure therapy since the need for aggressive reinterventions and the number of days of hospital stay may be reduced. Our series used negative pressure therapy in 11 patients, with a mean of 10.78 ± 10.01 days of use of the treatment with an average of between one and three changes per patient, with a mean hospital stay of 30.50 ± 19.86 days in the patients with the use of negative pressure therapy versus 20.07 ± 13.66 in whom it was not used. In the pairwise analysis, no statistically significant difference was found in hospital stay days with or without negative pressure therapy with p = 0.132. It should be noted that the historical bias must be considered since, prior to 2016, negative pressure therapy was not employed in our institute, as we did not have it. In the same way and added to the limitation of being a retrospective study, an analysis of a larger sample will be necessary, for which it is unnecessary to resort to the paired analysis of the sample. At the same time, it was recorded that the most significant number of reinterventions was in these patients. However, the procedure to be performed was replacing negative pressure therapy, which is not a major surgical procedure. Although it is performed in the operating room at INER, it is a procedure that can be performed safely in the patient's bed. It will be necessary to expand the sample with future cases to decide if a difference is observed in the days of hospital stay in the patients upon whom it is used versus those cases where it is determined not to use it.

Unquestionably, aggressive surgical drainage is essential for successfully managing DNM,[3] since broad-spectrum intravenous antimicrobial therapy is fruitless without effective drainage of the cervical region and mediastinal collections.[1] Failure to achieve complete and adequate mediastinal drainage is associated with an increased risk of death.[10]

Most authors decline the sole use of cervical drainage. Most agree that this approach does not allow complete visualization of the mediastinum and, therefore, adequate

Figure 2: Computed tomography of the chest with intravenous contrast in sagittal section, with data of ENDO IIB mediastinitis, with fluid and gas collections at the cervical level, anterior and posterior mediastinum.

excision of necrotic tissue.[3] In 1983, Estrera *et al.* recommended transthoracic drainage for mediastinitis that extends below the fourth thoracic vertebra in the posterior plane since it has been associated with more complications, such as increased pleural empyema.[1-4,17,18] Wheatley *et al.* recommend the combination of cervical and mediastinal drainage before drainage through the subxiphoid approach, along with tracheostomy to secure the airway, since cervical drainage alone has a 70 to 80% failure rate leading to multiple reoperations, prolonged hospital stays and a mortality of almost 40%.[1,2,19] Other authors recommend aggressive mediastinal drainage through a standard thoracotomy as the optimal treatment for DNM, regardless of the mediastinal level.[16,20-22]

In our group of patients, the combined approach was the most used in a total of 39 (76.49%), with cervicotomy combined with median sternotomy being the most used in a total of 21 of them (41.17%), followed by cervicotomy combined with right thoracotomy in 16 patients (31.37%). Median sternotomy also appears to be feasible in DNM type I and IIA but inappropriate in type IIB because access to the posterior and basal compartments of the thoracic cavity is difficult, in addition to being associated with osteomyelitis and sternal dehiscence.[3,23,24] In our series, one patient (1.97% of the total and 4.76% of the patients who underwent sternotomy) presented osteomyelitis and sternal dehiscence, requiring chest wall reconstruction with pectoral muscle flaps.

Since the beginning of video-assisted surgery in the 1990s and the extension of its use in thoracic surgery, it has been considered a choice in the treatment of DNM. Roberts *et al.* reported a case of thoracoscopic drainage as an alternative for the first time in a patient with mediastinal abscesses secondary to esophageal perforation.[25] In 2004, Isowa *et al.* reported successfully managing a patient with DNM via Video Assisted Thoracoscopic Surgery (VATS). In addition, two other groups of authors reported the successful use of VATS in four and nine patients with DNM. Although thoracoscopic drainage has not been wholly described for managing DNM, thoracoscopic exposure allows adequate visualization of the posterior mediastinum with adequate drainage of the collections; likewise, mediastinal collections can be visualized and drained.[26-29] Mediastinoscopy-assisted drainage can also be helpful in selected cases.[29] In our group of patients, only 3.92% underwent minimally invasive surgery, with adequate postoperative results in both groups. It should be noted that each case must be individualized and consider the degree of mediastinitis and the mediastinal compartments involved to select the surgical approach of choice adequately.

After said management, the hospital's average number of postoperative days was 22.65 ± 15.6. As previously mentioned, there was no statistical difference between the minimally invasive versus open groups and the groups in which negative pressure therapy was or was not used *(Figure 3)*.

Figure 3: Control X-ray upon discharge of the patient without evidence of pleural effusion, without data of mediastinal widening, with sternal fixation.

Mortality rates remain high, ranging from 12.5 to 37.5% in most recently published series. The leading cause of death is multiple organ failure, for which intensive care unit (ICU) participation is essential. In most published series, long ICU and hospital stays are the rule for patients treated for DNM. The need for a second or even more surgical intervention is also high (33-100%) in most published series, especially after a first attempt to drain the mediastinum through the neck.[10]

In our series, postoperative complications occurred in nine patients (17.64%), with pulmonary thromboembolism in two of those (3.92%), acute myocardial infarction, acute renal failure, upper gastrointestinal bleeding, supraventricular tachycardia, sternal osteomyelitis, and right cord palsy in one patient, each (1.96%). In addition, there were 14 deaths (27.45%), the most common cause being a septic shock, coinciding with what has been previously reported in the literature. All deaths were recorded in patients who underwent cervicotomy + open approach (sternotomy or thoracotomy), and no deaths were recorded in patients who underwent thoracoscopy and negative pressure therapy; however, a strict relationship between the medical approach and mortality cannot be considered since we have a historical bias. In agreement with what has already been reported in the literature, mortality is associated with the clinical severity of the patient diagnosed with septic shock.

Since there is no standardized algorithm for the surgical management of DNM, the stage and clinical status of the

patients should be considered to carefully choose the type of surgery to be performed, as well as the surgical approach that allows the best drainage of the mediastinum and pleural cavities considering the possibilities of each hospital center. Thus, taking into account the data from our review and the current management of patients with DNM at INER, we recommend the following points: 1) a multidisciplinary approach in conjunction with pneumology, intensive care, anesthesiology, infectious diseases, and thoracic surgery; 2) timely diagnosis with CT, early introduction of broad-spectrum antibiotics, and early surgical programming; 3) aggressive surgical drainage, cervicotomy in patients with ENDO I mediastinitis and combined approach (cervicotomy + sternotomy or cervicotomy + VATS versus thoracotomy) in those with ENDO IIA and IIB mediastinitis; 4) the type of thoracic approach (sternotomy, thoracotomy, or VATS) should be decided based on the hospital infrastructure and equipment, as well as the surgeon's experience, as long as complete drainage and debridement of all involved mediastinal spaces are guaranteed.

CONCLUSIONS

DNM continues to have impressive morbidity and mortality rates of 30 to 40% or more, almost always attributed to delayed diagnosis and inadequate surgical drainage of the mediastinum. For this reason, DNM needs a multidisciplinary approach based on intensive care unit support, aggressive antibiotic therapy, and said drainage and debridement of the initial infection site and mediastinum, as the prognosis for the disease is poor if proper treatment is not received. The role of surgery is crucial. For a successful result, it is necessary to have extensive knowledge of the cervical and mediastinal anatomy and the routes of the spread of the infection.

The results of our series are similar to those reported in the literature, the approaches described were used according to the availability of resources over time, and both the hospital stay and mortality did not differ from what was reported in the literature.

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Review
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Endothelial dysfunction as a consequence of COVID-19

Disfunción endotelial como consecuencia de COVID-19

Brian Carrera-De la Cruz,* Arturo Orea-Tejeda,* Dulce González-Islas,* Rocío Sánchez-Santillán*

*Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico City, Mexico.

ABSTRACT. COVID-19 (coronavirus infectious disease 2019) is caused by the virus SARS-CoV-2 and it has been a major health public problem worldwide, with complications and more than a million deaths around the world. The virus is part of the *Coronaviridae* family, and beta coronavirus (β-CoV) genus. Possess several proteins that codify the RNA and take action in the pathogenesis of the diseases. COVID-19 can occur as an asymptotic disease or with symptoms like cough, shortness of breath, fever, pneumonia, pulmonary edema, severe acute respiratory syndrome (SARS), in some cases neurological and gastrointestinal symptoms, even death. SARS-CoV-2 has several manifestations, in this review, we collect information for most recent articles about gastrointestinal manifestations, endothelial function, and the molecules involved in it, likewise, sepsis and inflammatory disease, and how the virus can act in that disease. SARS-CoV-2 causes endothelial dysfunction by infection and replication in the endothelial cells, additionally, by inflammatory interleukins release. Such as sepsis SARS-CoV-2 causes coagulopathy disorders; platelet aggregation, micro thrombosis, and severe complications, showing in a dimer D increased, and prothrombin time prolongation. Therefore, the aim of this article is to collect recent information available about the effect of SARS-CoV-2 on different organs, mainly gastrointestinal and endothelial function.

Keywords: SARS-CoV-2, COVID-19, endothelial dysfunction, thrombosis, coagulation disorders.

RESUMEN. La COVID-19 (*coronavirus infectious disease 2019*) es una enfermedad causada por el virus SARS-CoV-2 y ha sido un problema de salud a nivel mundial, con mayor morbilidad y mortalidad. El virus pertenece a la familia *Coronaviridae*, perteneciente del género betacoronavirus. (β-CoV). Posee proteínas específicas que codifican el RNA viral y toman acción en la patogénesis de la enfermedad. La COVID-19 puede cursar de manera asintomática o presentar los siguientes síntomas: tos, disnea, fiebre, neumonía, edema pulmonar, síndrome de insuficiencia respiratoria aguda (SIRA), en algunos casos síntomas gastrointestinales, neurológicos, incluso la muerte. El virus SARS-CoV-2 tiene diferentes manifestaciones a nivel sistémico, en este artículo se recopila la más reciente información sobre las manifestaciones gastrointestinales, función endotelial y sus moléculas, así como la relación entre el SARS-CoV-2 y la enfermedad inflamatoria y sepsis. El SARS-CoV-2 afecta al endotelio a través de la infección y replicación en las células endoteliales, además de generar una liberación de interleucinas inflamatorias. Así como la sepsis, el virus puede causar trastornos de la coagulación como agregación plaquetaria, microtrombosis y complicaciones más severas, demostradas en el incremento en el dímero D, y tiempos de coagulación prolongados. El objetivo de este estudio es resumir la información actual disponible acerca del SARS-CoV-2 en diferentes órganos y la función endotelial.

Palabras clave: SARS-CoV-2, COVID-19, disfunción endotelial, trombosis, alteraciones de la coagulación.

INTRODUCTION

COVID-19 (coronavirus infectious disease 2019) is caused by the virus SARS-CoV-2 and it has been a major health public problem worldwide with complications, and more than 500,000 deaths around the world. The virus is part of the *Coronaviridae* family, and beta coronavirus (β-CoV) genus, possesses several proteins that codify the RNA and takes action in the pathogenesis of the diseases.[1]

The pathogenesis of the virus depends on the receptor angiotensin-converting enzyme 2 (ACE2), a cell surface receptor that is present in a greater proportion in the lung and small intestine. The S protein is responsible for binding with ACE2 through the transmembrane protease receptor serine (TMPRSS), mainly in type 2 pneumocytes. The estimation of the COVID-19 incubation period is from 1 to 14 days from the first contact to the onset of symptoms.[2]

SARS-CoV-2 can occur as an asymptotic disease or with symptoms like cough, shortness of breath, fever, pneumonia pulmonary edema, severe acute respiratory syndrome (SARS), and in some cases neurological and gastrointestinal symptoms[3] even death.[1]

Correspondence:
Rocío Sánchez-Santillán MSc.
Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico City, Mexico.
E-mail: rnsanchezs@gmail.com

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SARS-CoV-2 and gastrointestinal system

SARS-CoV-2 can infect the cells of the gastrointestinal system due to the high proportion of ACE receptors and TMPRSS 2 in the esophagus, liver, and colon. It has been noticed a relationship between the expression of amino-acid transporters in the small bowel, and ACE2, this abnormality is related to enteritis and the loss of important amino acids in the human body.[4]

For the attachment of the virus into the cell membrane and the ACE2 receptor, it needs to break up into two parts (S1 and S2), this split is made by the serine protease, facilitating the endocytosis. Bound to the ACE2 receptor, there is an amino acid transporter B0AT1, when the SARS-CoV-2 blockage the membrane receptor ACE2, also block the B0AT1, reducing the transport of amino acids like tryptophan, which is important for the production of the antimicrobial peptide, likewise, citrulline malabsorption, which is important for the endothelial function.[5]

An altered intestinal microbiome combined with inflammation, increased the intestinal permeability, allowing toxin and bacterial translocation to the systemic circulation, this can contribute to multiorgan dysfunction.[6]

In some studies of mice infected by SARS-CoV, there have been such manifestations of GI tract damage, especially in the small bowel with enterocyte desquamation, edema, lymphocyte infiltration, and small vessel dilatation, also severe hemorrhage in the mesenteric ganglia and necrosis.[5,6]

Once the virus is in several organs, type II pneumocyte, endothelial cells, smooth muscle, macrophages, leads to inflammation by overproduction of pro-inflammatory cytokines, macrophages recruitment, and pro-inflammatory granulocytes producing a cytokine storm, endothelial dysfunction, microthrombi, small pulmonary vessel obstruction, vascular tone modification and thrombosis in several vascular territories.[4] The virus is easily spreading through several organs, one of the most important organs in which acts is the endothelial function.

Endothelial function

The endothelial cells are the main component of the blood vessels internal layer, it works to maintain the separation between the bloodstream and the extravascular tissues.[7] Endothelia is the main regulator of vascular homeostasis, the balance between vasoconstriction and vasodilatation, inhibits the proliferation/migration of the vascular smooth muscle cell, also modulates the hemostasia.[8]

Endothelial dysfunction can cause a lower expression of vasodilatory and antithrombic molecules; this is one of the characteristics associated with SARS-CoV-2 and the altered endothelial cell membranes. Additionally, generalized vasculopathy microangiopathy thrombosis and alveolar-capillary occlusion have been found in the lungs of COVID-19 patients.[9]

Microvascular and macrovascular severe dysfunction combined with immune overreaction can disrupt the atherosclerotic plaques and induce ischemic events, such as acute coronary syndrome.[2,8]

The main component for the vasodilatation in the endothelium is made by the action of nitric oxide (NO), thorough the precursor L-arginine catalyzed by endothelial nitric oxide synthase (eNOS), resulting in nitric oxide and L-citrulline.[8]

L-citrulline

L-citrulline is a natural precursor for L-arginine helping to *de novo* synthesis of it. It is an amino acid product from the metabolism of glutamine. At the same time, it can help to greater the production of nitric oxide.[10]

It is effective in cardiovascular function associated with endothelial function, such as hypertension, heart failure, atherosclerosis, diabetic vascular disease, and ischemic-reperfusion injury. One of the differences with L-arginine is that L-citrulline is not metabolized by the intestine either the liver and it does not induce the tissular arginase, on the contrary, inhibits its activity. Another characteristic of L-citrulline is its metabolism in the kidney, which also can transform into L-arginine increasing the plasmatic and tissular levels of L-arginine.[10]

It has been shown that L-citrulline has shown promise to be a good intervention to reduce the arterial tension (both at rest and induced by stress) in adults with pre and hypertension, also with experimental evidence, it can protect against atherogenic endothelial damage.[11]

Sepsis, inflammatory disease and their relationship with endothelial function

Inflammatory disease and sepsis are characterized by organic dysfunction, as a consequence of poor blood flow and a low vascular peripheric resistance, particularly at the microcirculatory site, resulting in inflammation and endotoxemia. Likewise, there is an association between sepsis and a reduction in the L-arginine levels, turns it over into a semi-essential amino-acid during stress condition such as sepsis.[12]

It has been shown that IL-6 plays an important role by suppressing the endothelial nitric oxide synthase (eNOS) function and induce the expression of tissular mononuclear cellular factor, as a result, the activation of the coagulation pathway and thrombin production.[13]

In an experimental study with sepsis-induced in Wistar rats, it was shown that the administration of

L-citrulline reduces the IL-6 levels, suggesting that it can help to increase the nitric oxide production; promoting microvascular dilatation and as a consequence, avoiding the tissular hypoxia and diminishing the intravascular coagulation activation.[14]

In another study with L-arginine and L-citrulline supplementation over the endothelial function of children and adolescent with mitochondrial diseases; L-arginine or L-citrulline were administered depending on the weight (500 mg/kg/day, in < 20 kg and 10 g/m^2 body surface area, distributed in three doses, respectively), in both groups, it was shown an increase in reactive hyperemia, therefore, an improved over the endothelial function.[15]

An interesting point is the fact that the endothelial cells of the lung arteries do not express the enzymes required for the production *de novo* of L-citrulline, therefore the intracellular concentration depends on the L-citrulline circulating. There is limited information about L-citrulline carriers on the pulmonary endothelial cells.[16]

Sodium natural amino acid transporters (SNAT) are one of the responsible systems of neutral amino acid transport. Due to the potential role over the L-citrulline transporter, it can evaluate the expression of SNAT on lungs, pulmonary arteries, and pulmonary arteries endothelial cells (PAEC) of newborn piglets.[16-18] The main SNAT expression founded over pulmonary arteries and lungs in those piglets were the SNAT 1, 2, 3, and 5.

Dikalova evaluates the function of SNAT1 over the PAECs newborn piglets and they found that hypoxic *in vitro* increases the absorption of L-citrulline; SNAT1 was identified as a responsible transporter of L-citrulline over hypoxic PAEC and their disposal. Likewise, SNAT1 silences the RNA, reduces basal nitric oxide production, and prevents the L-citrulline-induced elevations in no productions in both normoxic and hypoxic PAECs. Those findings suggest that an increase in the SNAT1 and a major transport of citrulline can participate in the no signaling during chronic pulmonary hypertension induced by hypoxia.[16,17,19]

In newborn piglets model with induced pulmonary hypertension show that L-citrulline treatment increases the production of pulmonary vascular NO, and decreases the elevation of vascular resistance pulmonary.[18]

Also, there have been found that the L-citrulline in a subcutaneous administration improves the pulmonary vasculature remodeling, and reduces the right ventricular hypertrophy, those cardiovascular abnormalities are associated with pulmonary hypertension. This could suggest that the use of L-citrulline can be used in humans with a high risk for developing pulmonary hypertension.[16,20]

In humans, it has been shown an improvement over the left ventricular ejection fraction, functional class, and endothelial function evaluated by photoplethysmography after four months of L-citrulline treatment. Moreover, it has been found an improvement in endothelial function in diastolic heart failure patients with 60 days of treatment.[21] Another study with obesity and hypertension or pre-hypertension found a reduction over the ankle blood pressure (endothelial function) and carotid augmentation index with watermelon extract supplementation as the main source of L-citrulline after six weeks of it.[22]

There are biomarkers associated with endothelial dysfunction including proteases, vascular adhesion cellular molecule (VCAM), glycocalyx components, coagulation factors such as tissue factor, plasminogen activator inhibitor type 1 (PAI1). During inflammation, there is a release of integrins and selectins associated with endothelial cellular activation. Those biomarkers can be benchmarks for the development of sepsis.[23]

In addition, the endothelial glycocalyx is a layer with a thickness from 1 to 3 µm covering the luminal membrane. It has been associated with pathologies like sepsis and there has shown damage to it, with oxidants, hyperglycemic, cytokines, and bacterial endotoxins.[24]

The glycocalyx detachment happened because of reactive oxygen species (ROS) as hydrogen peroxide, hydroxyl anions, and superoxide, heparinase and tumor necrosis factor also can participate in it. As a consequence, the endothelium increases the degradation products, and barrier function is lost, this is associated with edema, and contributes to organic failure induced by sepsis, it can be reverted with antioxidants like catalase and superoxide dismutase (SOD).[24]

There have been evaluated other molecules like syndecan-1, heparan sulfate, heparinase, endocan, and angiopoietins, and they are used as a sepsis diagnosis tool. The levels of syndecan-1 have been associated with endothelial damage, and glycocalyx degradation. Steppan and cols. evaluates the levels of syndecan-1 in 104 patients with septic shock, 28 patients with abdominal surgery and 18 healthy volunteers. The syndecan-1 levels were extremely high in sepsis and surgery groups than in the healthy group.[25]

Heparanase is a molecule associated with metastasis cases, also elevated in pulmonary and renal insufficiency with sepsis.[25]

Endocan also called Endothelial cell-specific molecule-1 (ESM-1) is a soluble proteoglycan expressed during an inflammatory state and it has been shown as a biomarker of endothelial dysfunction in sepsis. Endocan was associated with severe sepsis and was significantly associated with 30 days and 6 months of mortality.[26]

Endothelial function and COVID-19

One of the main characteristics of severe COVID-19 patients is the activation of the clotting pathway with

the possible development of disseminated intravascular coagulation (DIC). Also, linked to activation and dysfunction of the endothelial cells, as a consequence of the integrity of vascular loss and the endothelial cells death of the membrane cell, which is thrombogenic and activates the coagulation cascade.

The coagulation pathway is activated by interleukin-1ƒÀ and tumor necrosis factor (TNF) expressing selectin-P, Won Willebrand factor, and fibrinogen, binding with platelets. Moreover, endothelial cells release trophic cytokines increasing the platelet production and releasing vascular endothelial growth factor (VEGF), which acts over endothelial cells increasing tissue factor expression (principal activator of the coagulation cascade). As a response, the body organism develops several mechanisms to degrade the fibrin clots, this can explain the high levels of fibrin degradation products, which are associated with the worst prognosis.

As a whole, the small vessel congestion, DIC, and thrombosis over large arteries develop ischemic of the pulmonary tissue, unleash angiogenesis, and possible endothelial hyperplasia. The last one can help to exacerbate the mechanism of ischemia, nonetheless, angiogenesis can reduce it. The new vessels can promote inflammation by acting as ducts for inflammatory cells which are attracted by activated endothelial cells.[27]

All of the above can contribute to pulmonary microvascular thrombosis, bronchoalveolar fibrin deposits (a characteristic of the acute distress syndrome of the adult), and thromboembolic complications with a massive release of Von Willebrand factor and plasminogen activator.[28]

COVID-19 can disrupt the endothelial system, causing a massive release of won Willebrand factor (VWF), favoring thrombosis. The propagation of it is facilitated by the inflammation, the endothelial dysfunction which releases Il-6 as a response to the virus, amplifying the host immune response, causing the cytokines torment.[29] Although the vasculitis of the immune complex is part of the pathology of COVID-19, however, there is not enough evidence of it. The activation of the coagulation cascade on COVID-19 predisposed the coagulopathy induced by sepsis (CIS) and disseminated intravascular coagulopathy.[29]

Also, COVID-19 was associated with hyperviscosity. According to Cheryl *et al*. with 15 patients with COVID-19 pneumonia diagnosis and admitted to the intensive care unit, they found that all patients exceed 95% of plasma viscosity and this hyperviscosity was correlated with sequential organic failure (SOFA). Hyperviscosity is not only associated with thrombosis, moreover, with endothelial damage and dysfunction.[29,30]

Another hypothesis about the damage of COVID-19 is not only the macrovascular damage, moreover is focused on the microvascular and the NETs (tissue factor and neutrophil extracellular traps), they predispose to thrombosis and one of their functions is to act as a scaffold for fibrin deposits. They have the potential to propagate inflammation and microvascular thrombosis, including the lungs of patients with acute respiratory syndrome. In 50 patients report with COVID-19, they show elevated levels of cell-free DNA, myeloperoxidase (MPO), and citrullinated histone H3 (cit-H3).[31,32]

NETs can work as a nest of fibrin in addition to the platelet's accumulation. Furthermore, it has been shown that VWF ex *vivo* interacts with extracellular DNA providing a possible link between NET and platelet interaction.

Bin Cai et cols., show a diminished in TNF-, IL-6, IL-1 ƒÀ, over the first stages of sepsis, in Wistar rats with cecal ligation puncture and L-citrulline.[33]

When TNF-amounts diminish, the leucocytes stimuli, and the endothelial cells for the inflammatory cytokines' pathway, are reduced too. As a consequence, the capacity to damage the glycocalyx also diminished and the platelet adhesion is favored by the p-selectin. L-citrulline can reduce IL-6 and it can help to reduce the micro thrombosis risk and the activity of the extrinsic pathway of coagulation.[14,33]

CONCLUSION

SARS-CoV-2 causes endothelial dysfunction by infection and replication in the endothelial cells, additionally, by inflammatory interleukins release.

Such as sepsis SARS-CoV-2 causes coagulopathy disorders; platelet aggregation, micro thrombosis, and severe complications, showing in a dimer D increased, and prothrombin time prolongation, although, a certain amount of thrombocytopenic by consume.

Those patients with sepsis, it has been demonstrated some damage in other organs like the heart, kidney, bowel, affecting the abortion of amino acids, among these, L-citrulline and as a consequence the L-arginine plasmatic level.

The L-citrulline administration can improve endothelial function and reduces the thrombosis caused by COVID-19.

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Review
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Chest X-ray in pediatrics. A systematic interpretation

Radiografía de tórax en pediatría. Una interpretación sistematizada

Brenda Aguilar-Viveros,* Margarita Zamora-Ramos,‡
Blanca Estela Martínez-Martínez,* Laura Patricia Thomé-Ortiz*

*Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City,
‡Hospital Regional de Xalapa «Dr. Luis F Nachón», Xalapa, Veracruz.

ABSTRACT. Reading the chest radiograph requires training and repetition. The basic projections are: left lateral and posteroanterior. It is recommended to follow an order in interpretation: patient identification, projection, description of the technique (using the mnemonics GERICA), review of soft tissues, bony parts, diaphragmatic dome, mediastinum, cardiac silhouette and finally the lung parenchyma; all this considering the differences in pediatric age (changes in the technique by age group, bone variations, normal values of the cardiothoracic index, presence of thymus, etc.). All this will help us not to overlook any alteration and get the most out of this study, which is present in the daily life of every clinician.

Keywords: chest radiograph, pediatrics, interpretation.

RESUMEN. La lectura de la radiografía torácica requiere de entrenamiento y repetición. Las proyecciones básicas son: lateral izquierda y posteroanterior. Se recomienda seguir un orden en su interpretación: identificación del paciente, tipo de proyección, descripción de la técnica (mediante la nemotecnia GERICA), revisión de partes blandas, partes óseas, cúpula diafragmática, mediastino, silueta cardíaca y al final, el parénquima pulmonar; todo esto considerando las diferencias propias en la edad pediátrica (cambios en la técnica por grupo etario, variaciones óseas, valores normales del índice cardiotorácico, presencia de timo, etcétera). Esto ayudará a no pasar por alto ninguna alteración y obtener el mejor provecho de este estudio, el cual se encuentra presente en el día a día de todo médico clínico.

Palabras clave: radiografía torácica, pediatría, interpretación.

INTRODUCTION

Chest radiography is a usual diagnostic instrument in pediatric patient care that provides timely information, hence the importance of proper analysis and interpretation. It is commonly said, «A picture is worth more than a thousand words». An adequate exercise in radiographic evaluation can provide dynamic information derived from a static image.[1]

Correspondence:
Brenda Aguilar-Viveros, M.D.
Hospital de Pediatría del Centro Médico Nacional Siglo XXI,
Instituto Mexicano del Seguro Social. Mexico City.
E-mail: dra.bren.neumopediatra@gmail.com

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Radiological technique

The routine radiological examination of the thorax makes two projections: posteroanterior (PA) and left lateral (L). They are performed with the patient standing or sitting, the PA at a focus-film distance of 1.8 meters, and the left side at 2 meters.

The correct exposure is achieved using kilovoltage peaks (kVp), ranging from 100 to 140, to reduce the radiation scatter index, visualize the bone structures with better density and, in turn, adequately identify the lung parenchyma and mediastinum. The image results from the sum of the passage of a polychromatic X-ray beam through an object that contains areas with different absorption coefficients, registering on the film the combination of the response to the intensity of the emitted light and the non-absorbed portion of radiation.[1-4] They are performed in maximum inspiration and in apnea.

In the chest X-ray, the mediastinal structures and the diaphragm overlap the lung parenchyma, so in a PA projection, we will have 40% hidden areas; therefore, a lateral projection is always recommended.[2-4]

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In patients with poor clinical conditions, infants, and uncooperative patients, frequent in the pediatric age, X-rays are taken in an anteroposterior projection (AP) and with portable equipment, with the drawback of obtaining images of low technical quality; since this projection is performed at a shorter focus-film distance, structures are magnified, and fewer sharp images are obtained.[5]

There are other radiological projections, such as expiratory radiography, which detects small pneumothoraxes and localized air trapping associated with foreign bodies, and the lateral decubitus projection with a horizontal beam that evaluates free fluid in the pleural cavity, among others.

Basic concepts and terminology

In conventional radiology, we have five densities: air, fat, water, calcium, and metal *(Figure 1)*.

Remember, **radiolucent** is any object, organ, or tissue that allows light to pass through it and translates as dark shades. While **radiopaque** is any object, organ, or tissue that does not allow the passage of light or puts resistance to the passage of light on it and translates as light shades in the radiological image.

Interpretation

There should be a systematized analysis in the interpretation of thoracic radiography. We suggest the following order:

1. Patient's name and date.
2. Projection.

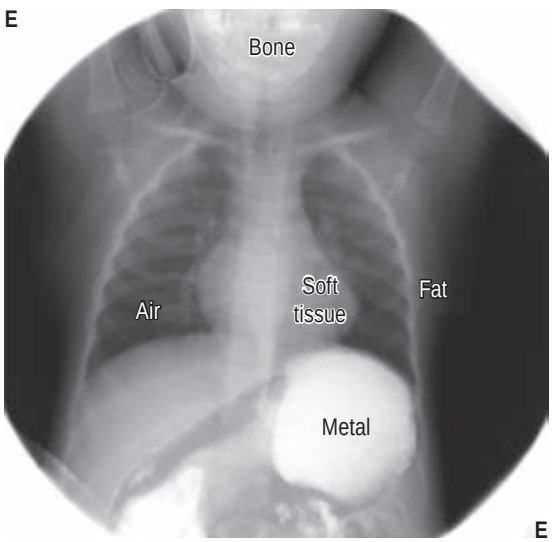

Figure 1: Radiological densities.
Image property of the author.

3. Technique (GERICA).
4. Soft parts.
5. Bony parts.
6. Diaphragmatic dome / costophrenic and cardiophrenic angles.
7. Mediastinum (carinal clarity, bronchi, thymus, hilar).
8. Cardiac silhouette.
9. Pulmonary parenchyma.
10. Pleura.

All radiological projections, including the lateral one, are interpreted in the same order.

1. Patient's name and date. First and essential step. On a printed radiograph, these data are found pointing to the patient's right side.
2. Type of projection.
3. Technique. Interpretation of the technical quality of the radiograph. The points to interpret are:

   GE: degree of exposure.
   R: rotation.
   I: inspiration.
   C: complete.
   A: artifacts.

We propose the GERICA mnemonic to remember them during the interpretation.

a. Exposure degree (GE): the thoracic spine should be visualized through the cardiac silhouette. If the film is underexposed, the diaphragm and lung bases will not become visible. The digital technique allows processing to adjust the exposure. A shorter exposure time will have a whiter appearance (underexposed). The longer the exposure time, the blacker (overexposed) will be appreciated. Avoid saying: burnt, soft, hard, black, or white.
b. Rotation (R): to determine whether the plate is rotated, the following methods are suggested: 1) measure the distance between the vertebral spinous apophyses and the medial ends of both clavicles, which should be equidistant;[3] 2) measure in both hemithoraxes the distance between the most medial portion of the anterior costal arches and the lateral contours of the spinal column.[6]
   The rotated side is the one that approaches the film. It does not matter if the projection is AP or PA.
c. Inspiration (I): the degree of inspiration will be adequate if the diaphragmatic dome or the cardiophrenic angles are projected over the seventh and eighth intercostal space or ninth posterior costal arch or, failing that, fifth or sixth anterior costal arch (eighth and fifth, respectively, in the neonate).[2,7]

The importance of adequate inspiration lies in the fact that the pulmonary structures are grouped in an exhaled radiograph and can simulate an alveolar lesion.[3]

d. It must be verified that the radiological image is complete (C); for this, the larynx and both costodiaphragmatic angles must be observed,[2] as well as the soft parts of the costal grill in its totality.
e. If artifacts (A) are present (probes, cannulas, catheters, etc.), they must be identified and described in the technique since they translate the degree of severity of the patients, and their clinical conditions, in addition to avoiding any interpretation error.

Radiological description

It is suggested to start with the parts from the least to the most interesting to avoid overlooking minor alterations.

4. Soft parts. The skin, subcutaneous tissue, muscles, and breasts make up the soft tissues of the rib cage and will behave like fat density. Intentionally look for emphysema, tumors, asymmetries, etcetera.[2]
5. Bone structures. Carefully observe the vertebrae and each of the ribs, looking for lesions. The morphology of the child's thorax changes as it grows. Thus, the thorax of the neonate has a trapezoidal morphology and horizontal ribs. In contrast, the thorax of the older child acquires the rectangular morphology typical of adults, with a larger vertical diameter.
6. Diaphragmatic dome/costodiaphragmatic and cardiophrenic angles. In 90% of the population,[6] the right diaphragmatic dome is usually about 2 to 3 cm higher than the left.[2] The continuity of the diaphragm should be visible in both AP and PA and lateral views. The costodiaphragmatic and cardiophrenic angles under normal conditions are acute and nearly symmetrical.
7. Mediastinum. It is an opaque region where we cannot differentiate the structures that make it up since most have water density and lose their limits between them. In a PA projection, the right mediastinal border from top to bottom is formed by the superior vena cava, right hilum, and part of the cardiac silhouette corresponding to the right atrium. The left subclavian artery, aortic button, left hilum, left atrial appendage, and left ventricle are on the left profile.
   a. Trachea: it is observed as a column of air between 5 and 7 cm at the level of T4 in infants and between 10 and 12 cm at the level of T5 in children older than three years. The diameter of the trachea remains constant, and its walls are parallel. It is common for children under five to observe lateral deviations due to their great flexibility. This physiological deviation is generally directed to the right, contrary to the direction of the aortic arch.[7]
   b. Bronchi: the left-side main bronchus is longer, and its bifurcation is greater than the right-side main bronchus, which is short and rapidly bifurcates into its lobar branches and is located behind the right pulmonary artery. This translates as bronchial situs solitus.[8]
   c. Thymus: it is an organ of soft tissue density, which projects to both sides of the superior mediastinum towards the fourth chondrocostal cartilage approximately. It may be visible in children under three years of age.[2] The radiological signs described are:
      - *Wave sign:* produced by the imprinting of the ribs on the thymus, visualized as a ripple.
      - *Sail sign:* homogeneous triangular radiopacity of the right and sometimes left side, with the major base adjacent to the mediastinal alignment and the apex downward and outward, like a ship's sail *(Figure 2)*.[2]
      - *Convergence sign:* the thymus covers the upper part of the cardiac silhouette like a cap, determining at the point of convergence of the two a notch on the right side, the left side, or both.
      - *Hilar overlay sign:* in marked hypertrophy of the right lobe of the thymus, the cardiac border and the structures of the right hilum can be seen through the thymic opacity.[2]
   d. Hilia: they form water density.[6] In 97% of cases, the left hilum is taller than the right one.[2]
8. Cardiac silhouette. For the evaluation of cardiac size, the cardiothoracic index *(Figure 3)* has been used, which has

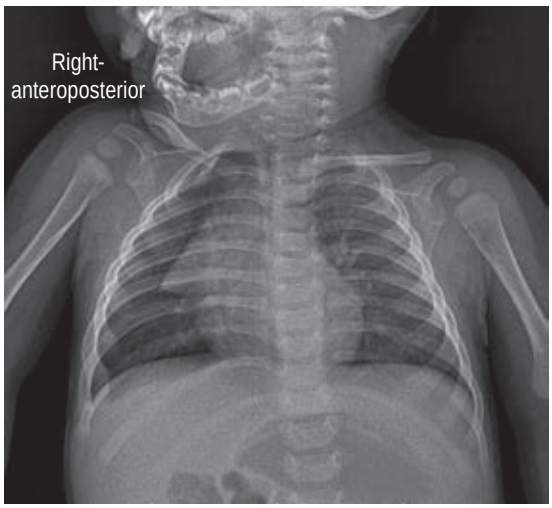

Figure 2: Sign of the thymic sail.
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different normal values by age group *(Table 1)*;[9-11] however, these measurements vary significantly between patients and in the projections since the AP projection magnifies the cardiac silhouette, giving an erroneous result, and should therefore be taken with reservation.[7,8]

9. Pulmonary parenchyma. The pathologic conditions that produce changes in the density of the lung parenchyma can be divided into those involving the alveolus, the interstitium, or both.[6] For its description, we will classify it in radiographic patterns:
   a. Alveolar pattern: the air in the alveoli is occupied by fluid, inflammatory exudate and/or cells, transudate, blood, or tissue. Radiological features include radiopaque images with a tendency to coalesce, cottony appearance at the edges, and lobar distribution.[4,6]
   In alveolar involvement, the bronchi remain aerated (radiolucent) and surrounded by consolidated parenchyma (radiopaque), and this conjunction of images evidences the bronchus and corresponds to the air bronchogram sign.
   b. Interstitial pattern: caused by diseases that affect the interalveolar septa involving the interstitial connective tissue and pulmonary capillaries without affecting the alveolar space. There are diverse ways of description through the following patterns:[7,12,13]
      - *Reticular pattern:* refers to multiple tiny radiopaque lines crisscrossing at various angles to create a lattice pattern.[13]
      - *Nodular pattern:* described as the presence of well-defined rounded radiopaque images of diffuse bilateral distribution, micronodular images are defined as those with a diameter of less than 5 mm, and macronodular images as those with a 5 to 3 cm diameter. The miliary pattern refers to diffuse bilateral symmetrical diffuse micronodular images of the same density and is generally related to tuberculosis with lymphohematogenous dissemination.[14]
      If an area of focal consolidation has well-defined borders and is larger than 3 cm, it is called a «mass». If it measures less than 3 cm, it is called a «nodule».[3]
      The reticulonodular pattern is a combination of both.
      Honeycomb pattern: it is characterized by the presence of thick reticular opacities, with interposition of clarities resembling cystic spaces. It represents the last stage of cicatrization.[12]
      - *Unpolished glass:* corresponds to a faint increase in density that does not hide the pulmonary vasculature but with poor definition of the vessel margins.[6]
   c. Atelectasis: it is described as an opacity of homogeneous character that presents a triangular image of a well-delimited border with medial or internal vertex and external base. For its identification, there are direct and indirect signs:

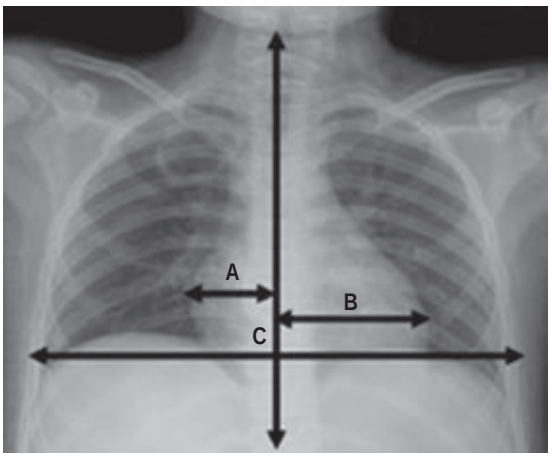

Figure 3: Cardiothoracic index measurement method. «A» is equal to the distance between the outermost part of the right cardiac border. «B» is equal to the distance between the outer part of the left heart border; the sum of A + B is divided by the diameter of the thorax at its widest point at the level of the diaphragms «C».
Image property of the author.

Table 1: Cardiothoracic index (CT) values at pediatric ages.[9-11]

Age	CT index	Range
0-3 weeks	0.55	0.45-0.65
4-7 weeks	0.58	0.46-0.70
1 year	0.53	0.45-0.61
1 a 2 years	0.49	0.39-0.60
2-6 years	0.45	0.40-0.52
7 years	< 0.50	0.40-0.50

Direct

1. Displacement of the fissures is the most reliable sign.
2. Clustering of pulmonary vessels or bronchi.
3. Loss of aeration (radiopacity).

Indirect

1. Elevation of the hemidiaphragm on the affected side.
2. Tracheal deviation towards the affected side.
3. Retraction of the heart towards the area of injury.
4. Narrowing of the intercostal space in the affected area.
5. Hilar retraction towards the area of injury.
6. Compensatory hyperinflation of adjacent lobes.[6,12]

d. Hyperclarities: they can be generalized or diffuse and localized. They correspond to two types of involvement: an increase in the size of the alveoli or their number and the absence of lung parenchyma, constituting cystic images or cavities.[2]
Cavities are limited by an opaque ring surrounding an area in which there are no alveoli and, according to their pathogenesis, can be classified into three:
Bullae: thin-walled cavities, single or multiple, which are characterized by varying shape, size, and location from one examination to another; they appear in sequels of abscesses, caverns, pneumonia, trauma, etc.[2]
Bullous pneumonia: characterized by the formation of a type of bulla called pneumatocele, formed by air leakage with cavity formation within a pneumonic process. They lack hydroaerial levels.[2]
Blebs or subpleural bubbles: small subpleural cavities located at the apexes, whose rupture can cause spontaneous or recurrent pneumothorax.[2]

e. Caverns and abscesses: thick-walled cavities with pericavitary condensation and, sometimes, liquid level. Unlike pneumatoceles, they are produced by necrosis of lung parenchyma, either from liquefaction (lung abscess and necrotizing pneumonia) or caseous (tuberculous cavern) and subsequent emptying of the cavity, for which they have a drainage bronchus. Pericavitary condensation happens because they always occur within pneumonia. The tuberculous cavern usually has a smooth internal border and low liquid level, and the abscess has an irregular inner border with a notable hydroaerial level.

f. Cysts: cavities of thick and uniform walls, surrounded by healthy parenchyma, and that do not vary in time or do so very slowly. If they have suffered complications, they may be empty or have a hydro-aerial level. If they are filled with liquid content, they have the appearance of a mass. They can be congenital, like the bronchogenic cyst, or acquired, like the hydatid cyst.

10. Radiological signs of pleural alteration.

a. Pleural effusion: free pleural fluid in the standing position tends to be in the posterior and lateral costophrenic angles, so they are more evident in the lateral projection; they lose their normal shape and are effaced *(Figure 4)*.[3]
If there is more fluid ascending through the pleural space, a meniscus is formed. Pleural fluid is often seen ascending through the greater fissure in the lateral projection; requesting a lateral decubitus projection with a horizontal beam is recommended, remembering that the affected side should be down.[3]
If a radiopaque hemithorax is found displacing the mediastinal structures, it is a pleural effusion or a tumor. If there is no displacement, it may be atelectasis.

b. Pneumothorax: radiological findings are peripheral hyperlucency (intrapleural air), visceral pleural line or border, and absence of peripheral vascular raster.[3] Pneumothoracic tension compromises pulmonary venous return and is a medical emergency. The three radiographic signs that indicate a tense pneumothorax are collapsed lung, descent of the hemidiaphragm, and contralateral mediastinal shift. The intercostal spaces on that side may be separated.[3]
There is no unification on the method for quantifying the size of the pneumothorax. Some established definitions are: small pneumothorax when the distance between the pulmonary apex and the thoracic dome is less than 3 cm.[15] On the other hand, the British Thoracic Society differentiates pneumothorax into small or large based on the presence of a band of air < 2 or > 2 cm, respectively, between the pulmonary border and the thoracic wall.[16]
The Rhea and Light criteria, illustrated in *Figure 5*, have been described in numerical terms to quantify pneumothorax.[17,18]

Figure 4: Left pleural effusion. Homogeneous radiopacity is observed in the left basal region, with erased costodiaphragmatic and cardiophrenic angles. Image property of the author.

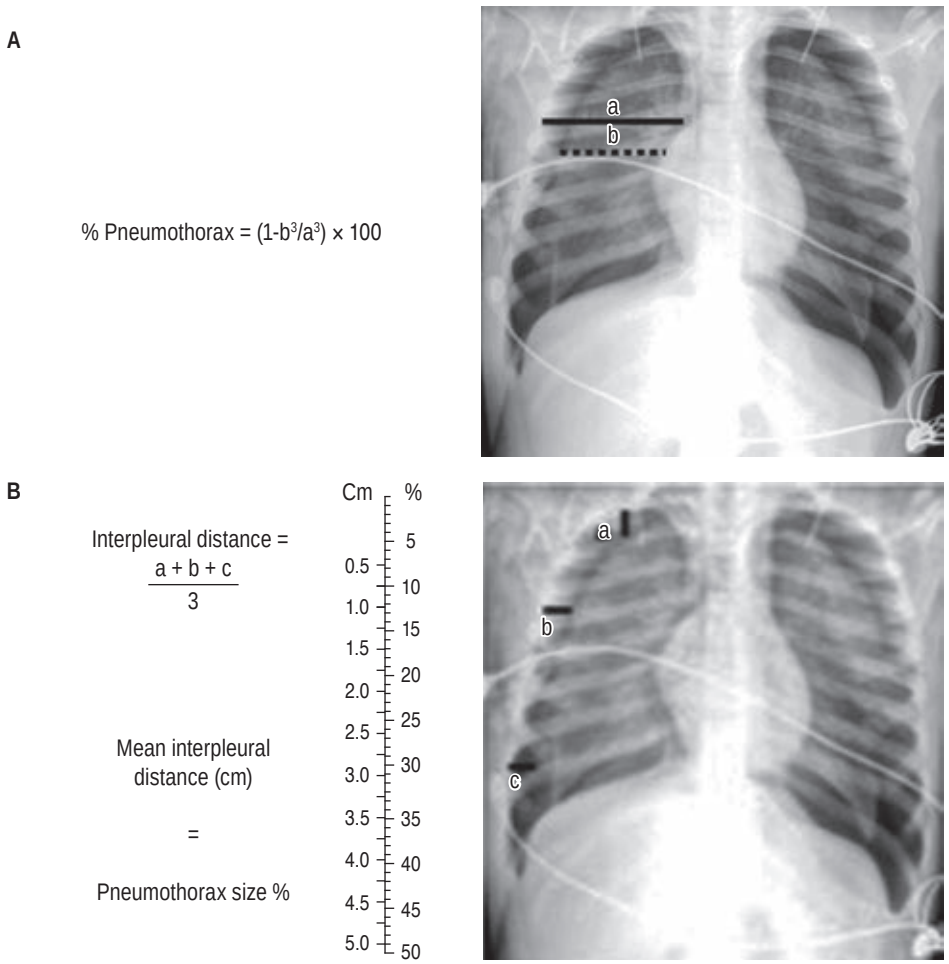

Figure 5:

Methods for calculating the size of the pneumothorax. **A)** Light's method. **B)** Rhea's nomogram.[17,18] The results represent the percentage of pneumothorax.
Images modified by the author.

CONCLUSIONS

Chest radiography is a particularly useful tool in the study of many pediatric pathologies and is part of the initial evaluation. Its proper interpretation can be the starting point in the suspected diagnosis. It is essential that it is performed systematically and that the differences inherent to the pediatric age are considered.

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Ideas and perspectives

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COVID-19: What about the lidership?

COVID-19: ¿Qué pasa con el liderazgo?

Luis Torre-Bouscoulet*

*Instituto de Desarrollo e Innovación en Fisiología Respiratoria (INFIRE). Mexico City, Mexico.

Each country, community or individual has experienced the SARS-CoV-2 pandemic differently according to its economic, social, cultural, health, family and religious particularities. In any case, the pandemic has exposed the enormous flaws in the health care system of almost every country. In Mexico, a series of unfortunate elements converge in varying proportions, including an environment of limited resources where magical thinking, superstition, misinformation, commercial and political interests, poor accessibility to health services and a long and painful etcetera prevail. The simultaneous participation of these and other factors explains —at least in part— why Mexico is one of the countries where the SARS-CoV-2 pandemic has caused the most devastation.[1] In addition, Mexico is the country quintessentially characterized by reactive and insufficient responses to complex, serious and multifactorial problems.

Despite the adverse scenario, there are aspects of the SARS-CoV-2 pandemic that could be considered favorable and used to improve respiratory health. A pulse oximeter is now available in a large proportion of Mexican households. Thousands of people are familiar with the term «oxygenation», indeed, they even know relatively well the percentage of normal oxygen saturation that an individual should have. This phenomenon of medical self-education under the health pressure of the pandemic is favorable for identifying at least the tip of the iceberg of hypoxemic subjects. Although the use of pulse oximetry in the management of patients with COVID-19 did not improve survival,[2] current knowledge about oxygenation is something that increases the population's sensitivity to respiratory disease. The same happens with the current popularity of chest X-ray or chest tomography that should be used in favor of the identification of patients not only with COVID-19, but also with chronic respiratory diseases (CRD) and be able to decrease its enormous underdiagnosis. It is desirable to use the current knowledge of the general population about these diagnostic methods to identify a greater number of patients with lung cancer, fibrosing diseases, emphysema, bronchiectasis, etcetera. Parallel campaigns to identify such patients could be very successful by taking advantage of the inertia gained from the COVID-19 pandemic.

In general terms, in Mexico, 90% of people with CRD are not diagnosed. The burden on the health system that they represent is gigantic, since when they go to the hospitals, they are usually in advanced stages of the disease with very few options for successful treatment.[3] In this sense, we must popularize other diagnostic tests related to respiration such as respiratory function tests and sleep studies.

Another positive aspect of the pandemic is that the general population's knowledge of the specialty of pulmonology has increased markedly. Until recently, people were well aware of the type of problems that an orthopedist, ophthalmologist or gynecologist treats; however, the specialty of pulmonology was practically unknown. Now, people know that the specialist in lung diseases is the pulmonologist. It seems a small thing, but in terms of medical education in the population, it is an ostensible advance. The population must create its own needs and demand the corresponding health services. The greater social recognition of the pneumology specialty is a factor that should be taken advantage of to manage human and technological resources for respiratory health.

Remote medicine —telemedicine or telehealth— is a beneficial strategy that has been greatly boosted by the pandemic. Most auxiliary diagnostic studies now have real-time connectivity to the internet; so that we can have

Correspondence:
Luis Torre-Bouscoulet, M.D.
Instituto de Desarrollo e Innovación en Fisiología Respiratoria (INFIRE). Mexico City.
E-mail: luis.torre@infire.mx

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oximetry, radiography, functional studies, tomography and sleep studies at our fingertips via smartphones. Artificial intelligence could even help in mass decision making without the need for a person to be on the other end of the line. The above represents unprecedented opportunities to advance respiratory medicine in our country and globally.[4]

Although from the point of view of health care, the participation of pulmonologists has been very important during the pandemic, their contribution to public health has been poor. The leadership of pneumologists should be a protagonist in public health decision making and health policies, in the distribution of resources, in the planning and implementation of massive respiratory health care strategies, in the development of research centers in emerging respiratory diseases, and in many other aspects such as the promotion of human resources training related to respiratory health. There is no doubt that there is a need to promote the training of pulmonologists and, for this reason, there are now a large number of training centers for pulmonologists throughout the country with direct entry; however, the strategy cannot only be quantitative, but also requires a qualitative approach. Once again, the reactive response appears, poorly planned, «on the fly», short term. The commitment cannot be as short-sighted as training more pulmonologists because Mexico needs them. More are needed, no doubt, but also better pulmonologists. Not only specialists who cover the primary need to care for patients, but also pulmonologists who are pioneers in their workplace or in their community, who teach, who are academics, who do research; in a word, who are leaders. A leader provides gigantic benefits to individual and collective health. These benefits often grow exponentially as the leader's professional development grows.

Current pulmonologist training sites created in the wake of the pandemic are poorly planned. They have one or two pulmonologists who are the professors and their program usually lacks university recognition. They do not have sufficient equipment to assist in the respiratory diagnostic process, that is, they do not have bronchoscopes, respiratory physiology equipment, diagnostic equipment for sleep disorders, etcetera. Staying in other hospitals does not solve the problem. Hospital centers that have all the diagnostic and therapeutic tools are not only overcrowded with patients, but also with trainees. Hand in hand with the above, there is the need to create more vacancies for pulmonologists in the country's public institutions. Training more pulmonologists on the fly without vacancies in the hospitals is nonsense. Every second level hospital should have at least one or two vacancies for specialists in respiratory medicine.

We must take advantage of the current situation of the pandemic and leave behind the conformist and mediocre thinking in order to promote pulmonologists in training as a priority. The history of the great Mexican institutions related to health was like that, betting on quality. Young specialists traveled to the United States or Europe with the support of the training hospital centers, to later return to exercise the intellectual leadership that contributed to the growth of the institutions and Mexican medicine. This has been almost completely lost. To remain with the idea that we are intellectually and technologically self-sufficient is, undoubtedly, a thought as parochial as it is arrogant. We may be self-sufficient in some disciplines, but when it comes to developing at the frontier of knowledge and technological advances, we need to expose ourselves to what is being done in medical and educational centers in developed countries. We must have the humility to understand and bridge the gap that separates us from those centers and, with everyone's talent, sublimate that gap and transform it into opportunities for growth. We must make respiratory medicine in Mexico evolve. Evolution implies, by definition, qualitative modification.

Now, with the pandemic on our shoulders, we must promote new generations of pulmonologists and bet on quality. This is the historic moment that Mexican pulmonology needed to take giant steps forward on the complex path of development. The urgency of the pandemic should not be the reason to put quantity before quality. The pandemic will not be solved because in five or six years we will have more pulmonologists with weak training and scarce vacancies for their recruitment. The vast majority of them will sadly join the large group of poorly competitive physicians we have in Mexico.

Management skills are the key. The greatness of the Mexican physicians who cemented the golden age of Mexican medicine was rooted in their management capacity. Ignacio Chávez, Salvador Zubirán, Donato Alarcón, Federico Gómez and all that generation of personalities, based their trajectory on the management capacity that their leadership granted them. They had the determination and perseverance to make things happen. From dreams they made realities. It does not matter if those professors were magicians when they hit the prechord or when they searched for the sign of the Pitres coin; their greatness was, without a doubt, their management capacity. They managed and achieved many things, but the most valuable aspect of their efforts —and common denominator in all of them— was the support and commitment to the quality of their doctors. Mexico owes them a golden era of achievements and successes that persist to this day. As Dr. Pelayo Vilar said in some of his splendid conferences: «I do not know if Mexico would be the same without the management of those giants of medicine, but what I am sure of is that it would not be better». How much we need that sense of leadership and

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that management capacity of those visionary doctors to move forward in the jungle of corruption and of a senseless Mexico.

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Clinical case
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Tracheal distal third perforation. A case report

Perforación del tercio distal de la tráquea. A propósito de un caso

Francisco Javier Armas-Zárate,* José Morales-Gómez,*
Juan Carlos Vázquez-Minero,* Edwin Gustavo Barrientos-Morales*

*Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico City, Mexico.

ABSTRACT. Perforation of the tracheobronchial tree is a potentially life-threatening clinical scenario. The most common causes are iatrogenic perforations. The incidence of this pathology is very low, making appropriate treatment challenging for the surgeon. Bronchoscopy is the gold standard for diagnosis. The most common site of iatrogenic perforations is usually in its proximal third. Treatment should be individualized to each clinical scenario. We present the case of a patient with tracheal perforation in the distal third evidenced by bronchoscopy, with progressive symptoms, who required emergency surgical management with resection and tracheal anastomosis, being its repair challenging due to the anatomical site which is not the most common presented in the literature. With adequate postoperative evolution of the patient. In cases of tracheal perforation and progressive symptomatology, surgical treatment plays a fundamental role.

Keywords: perforation of distal third of trachea, thoracic surgery, trachea, case report.

RESUMEN. La perforación del árbol traqueobronquial es un escenario clínico que amenaza potencialmente la vida. Las causas más comunes son las perforaciones iatrogénicas. La incidencia de esta patología es muy baja, por lo que el tratamiento adecuado es desafiante para el cirujano. La broncoscopia es el estándar de oro para el diagnóstico. El sitio más común de las perforaciones iatrogénicas suele ser en su tercio proximal. El tratamiento debe ser individualizado a cada escenario clínico. Se presenta el caso de una paciente con perforación traqueal en tercio distal evidenciado por broncoscopia, con síntomas progresivos, que requirió manejo quirúrgico de urgencia con resección y anastomosis traqueal, siendo desafiante su reparación por el sitio anatómico que no es el más común que se presenta en la literatura. Con adecuada evolución posoperatoria de la paciente. En los casos de perforación traqueal y sintomatología progresiva, el tratamiento quirúrgico tiene un papel fundamental.

Palabras clave: perforación tercio distal de tráquea, cirugía torácica, tráquea, reporte de caso.

INTRODUCTION

Perforation of the tracheobronchial tree is a potentially life-threatening clinical scenario.[1] The most common causes are penetrating or blunt trauma in 28% and iatrogenic perforations in 58% of cases.[2] The incidence of this pathology is often underestimated and underreported.[1] Iatrogenic perforations are a rare complication of orotracheal intubation, percutaneous tracheostomy and rigid bronchoscopy, with an incidence of 0.05 to 0.5%.[3] Risk factors are divided into mechanical and anatomical. Among the first ones are tracheal instrumentation (rigid bronchoscope, balloon dilatation, among others), emergency orotracheal intubation, female sex and age over 65 years. Among the anatomical factors, congenital abnormalities and tracheal inflammation due to infection or immune pathologies are relevant.[1]

The clinical presentation of this pathology is nonspecific. Typical findings are subcutaneous emphysema, pneumomediastinum and pneumothorax. Other signs may include respiratory failure, hemoptysis or shock. Its presence will depend on the clinical scenario and the time of presentation may be immediate or delayed.[1] A high degree of clinical suspicion is important to establish the diagnosis. Imaging studies, mainly computed tomography (CT) may reveal findings suggestive of tracheal rupture such as pneumomediastinum, subcutaneous emphysema, pneumothorax or tracheal rupture itself.[1] The use of imaging studies depends on the stability of the patient and the availability of hospital resources. The gold standard for diagnosis is bronchoscopy. Bronchoscopy helps identify

Correspondence:
Francisco Javier Armas-Zárate, M.D.
Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico City, Mexico
E-mail: drfco07@hotmail.com

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the exact site and size of the rupture; and in some cases treatment, depending on the degree of rupture.[1]

As for the location of the tracheal rupture, it will depend on the etiological mechanism.[1] In rupture of iatrogenic cause, the most common form is the rupture in the membranous portion of the cervical and thoracic segments of the trachea.[1] The most commonly used morphological classification for iatrogenic lesions is the one proposed by Cardillo *(Table 1)*.[1,4]

Treatment should be individualized according to the patient's comorbidities, clinical presentation and anatomy.[1,5,6] In grade I and II ruptures, conservative treatment is generally chosen depending on the patient's stability.[1,5] While in grade III ruptures, surgical management is usually chosen; however, nowadays, with the use of minimally invasive devices, stent placement can be chosen in some selected cases.[1,5]

There are no specific guidelines on surgical treatment in patients with tracheal rupture. Traditionally, most experts agree that in rupture larger than 4 cm and in those patients with clinical deterioration surgical treatment is indicated.[1,6,7] Most authors also conclude that surgical treatment should be the first choice of treatment for iatrogenic airway injuries.[1,6,7]

In patients with progressive subcutaneous emphysema, pneumomediastinum, pneumothorax, persistent air leak or lack of lung expansion despite endopleural tube placement, emergency surgical treatment is indicated.[1,5] The surgical approach depends on a variety of factors, including location of the tracheal perforation, either in the proximal 2/3 or distal third, including main bronchi; as well as the presence or absence of vascular or other concomitant organ injury. For any surgical approach it is important to gain adequate exposure to examine adjacent organs for damage.[1,7]

If the perforation involves the proximal 2/3 of the trachea, the repair can be via the cervical route.[1,5] If the middle third is involved, the incision can be extended in a T-shape, with opening of the sternal manubrium.[1,5,7] Perforations involving the distal 1/3 of the trachea and the carina or any of the main bronchi can be approached via right thoracotomy, with a median sternotomy being an option.[1,5,7]

The most relevant prognostic factors for mortality in these patients are the extent of tracheal perforation (greater than 4.5 cm) and the development of mediastinitis.[8]

We report a challenging case due to the site where the tracheal stenosis was located (distal third), which is the least common and due to the low frequency and the scarce availability of guidelines on the subject, many authors recommend the approach according to the experience of the surgeon in charge. In addition, the context in which the perforation occurs, with limited ventilation and the impossibility of having a Y stent, as a possibility of endoscopic management, meant that this case had immediate surgical management.

Table 1: Morphological classification of Cardillo's tracheal rupture.[1,4]

Grade	
I	Mucosal or submucosal rupture without mediastinal emphysema or esophageal perforation
II	Rupture extending into the muscle wall with subcutaneous or mediastinal emphysema without esophageal perforation or mediastinitis
IIIA	Complete rupture with mediastinal or esophageal soft tissue herniation without esophageal perforation or mediastinitis
IIIB	Any rupture with esophageal perforation or mediastinitis

CASE PRESENTATION

A 36-year-old woman. History of prolonged orotracheal intubation for 60 days, without tracheostomy, 10 years ago secondary to hemorrhagic shock due to ectopic pregnancy that required left oophorectomy. Prolonged hospitalization for hospital pneumonia and critical patient myopathy, with hospital discharge 14 months later. Subsequently with progressive dyspnea and stridor. She was evaluated two years later by thoracic surgery who diagnosed tracheal stenosis and performed fibrobronchoscopy and mechanical tracheal dilatation three times in a period of one year.

Subsequently, she was referred to a tertiary hospital where she was followed up conservatively. A year ago, she presented with progressive dyspnea and stridor, for which she was referred to the Instituto Nacional de Enfermedades Respiratorias (INER) Ismael Cosío Villegas, Mexico City. A revision fibrobronchoscopy was scheduled, which showed tracheal stenosis to nine tracheal rings of the vocal cords, 1.5 cm long, with four free tracheal rings to the main carina; hydrostatic balloon dilatation was performed, achieving a post-dilatation lumen of 80%. Due to recurrence of symptoms, the patient underwent a new fibrobronchoscopy one month later. It was decided to approach with rigid bronchoscopy to dilate the stenosis and a granuloma was observed at the end of the stenosis, which was resected with biopsy forceps, after which a perforation was observed in the right lateral face of the trachea of approximately 0.5 cm to a main carina ring. The patient started with progressive subcutaneous emphysema, with difficulty in mechanical ventilation, so it was decided to perform a median sternotomy to repair the perforation. She was not considered a candidate for endoscopic management with stent, due to the proximity of the perforation to the carina and the need for a Y-stent, which is not available at the institute. Tracheal perforation was found at the level of the

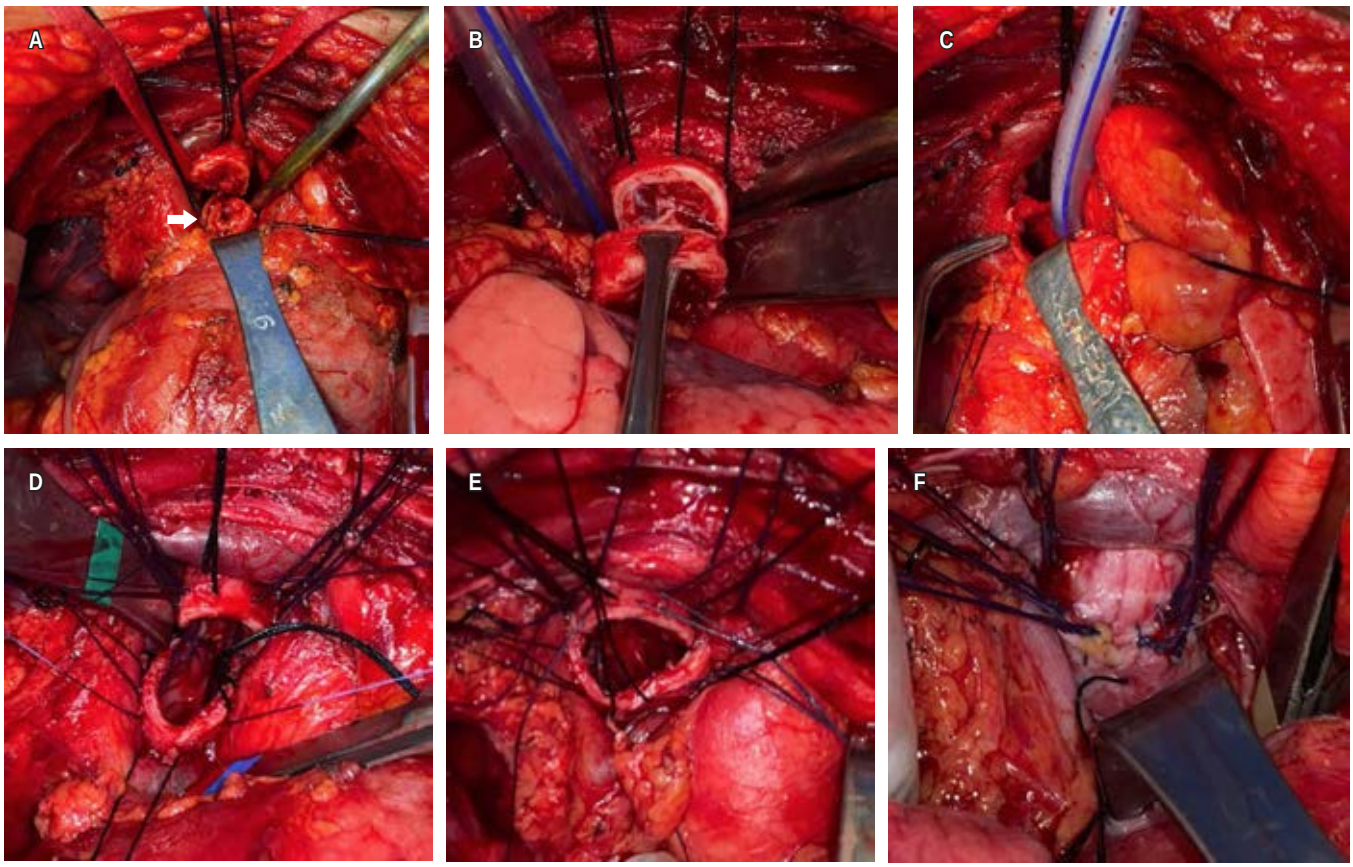

Figure 1: Transoperative images. **A)** Tracheal stenosis at the level of the distal third of the trachea occluding 80% of its lumen (arrow). The median sternotomy approach is demonstrated. **B)** Resection of the tenth to twelfth tracheal ring affected together with the perforation site. **C)** Use of selective cross mechanical ventilation to the right main bronchus, due to the proximity of the perforation to the main carina. The left main bronchus is observed. **D)** Posterior face of tracheal terminoterminal anastomosis with separate stitches. **E)** Anterior face of tracheal anastomosis prior to closure. **F)** Finished tracheal anastomosis.

eleventh tracheal ring of 0.5 cm in length, so it was decided to perform resection of the stricture site from the tenth to the twelfth tracheal ring, with terminoterminal anastomosis between the ninth and thirteenth tracheal ring without tension *(Figure 1)*. Associated esophageal perforation was ruled out with transoperative endoscopy. She passed the postoperative period without complications. Endopleural and mediastinal probes were removed on the fifth day. Hospital discharge was on the seventh day. No respiratory symptoms at six months' post-surgery, evidenced by control spirometry, within normal parameters, and clinically without stridor and with adequate phonation.

DISCUSSION

Tracheobronchial tree perforation is a medical-surgical emergency that requires a rapid response from the surgical and anesthetic team to achieve adequate patient outcomes.

The gold standard for diagnosis is bronchoscopy. In this case the perforation occurred during tracheal instrumentation, so the diagnosis was made at the time of the procedure.

Signs and symptoms may vary in the presentation of tracheal perforation due to the time and form of presentation. In our case, the signs were immediate (subcutaneous emphysema in the neck, thorax and abdomen, in addition to leakage in mechanical ventilation with difficulty in ventilation) with a rapid evolution, which led to emergency surgical management.

Depending on the time of evolution, site of perforation and experience of the surgical team, different approaches can be performed. In the literature, right thoracotomy is proposed as the approach of choice for distal third perforations. In this case, a median sternotomy approach was chosen, since rapidly progressive symptomatology was presented, and therefore it was considered that the sternotomy had a better field of exposure for surgical resolution.

The type of repair will depend mainly on the extent and conditions of the particular patient. In our case it

was a grade IIIA Cardillo perforation *(Table 1)*, so it was not considered for endoscopic treatment. The repair was with resection and terminoterminal anastomosis, since the underlying pathology was a benign post-intubation tracheal stenosis, and when the perforation was present within the segment with stenosis, it was decided to resect the entire affected part.

In this case she was not considered a candidate for endoscopic management, due to the proximity of the perforation to the tracheal carina, which would require a Y-stent, which is not available at the institute; however, if available, it is a viable option. The patient had no risk factors for short-term mortality. The good functional status, perforation with short extension (0.5 cm) and rapid treatment contributed to the adequate evolution.

The approach to complex tracheal stenosis will always be recommended in hospitals with trained and experienced thoracic surgeons in the definitive treatment and resolution of possible complications such as tracheal perforation.

CONCLUSIONS

The approach and treatment of the patient presenting with a tracheobronchial tree perforation depends on multiple patient factors and the hospital environment. A multidisciplinary team with experience in the appropriate management of these patients is recommended. Adequate airway control and, regardless of the approach, adequate repair of the perforation is essential, which leads to better patient survival rates and lower morbidity and mortality.

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Esophageal balloon in ECMO: clinical case report

Balón esofágico en ECMO: reporte de caso

Venus Nefte López-Zamora,* Ismael Maldonado-Beltrán,* Gustavo Lugo-Goytia,* Carmen Margarita Hernández-Cárdenas*

*Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico City, Mexico.

ABSTRACT. Severe respiratory distress syndrome, which does not respond to conventional strategies, benefits from veno-venous extracorporeal membrane oxygenation therapy. This bridging therapy can be complemented with lung ultra-protection maneuvers. Transpulmonary pressure may help reduce the risk of ventilator-induced lung injury due to atelectrauma. However, its benefit remains to be established. We present the case of a 34-year-old man with severe acute respiratory failure syndrome receiving veno-venous extracorporeal membrane oxygenation therapy and ultrapulmonary protective ventilation, with positive end-expiratory pressure titration by transpulmonary pressure. Veno-venous extracorporeal membrane oxygenation was successfully decannulated after adequate resolution of the acute respiratory distress syndrome. In this case, it was possible to observe that a ventilation strategy that uses esophageal pressures to estimate transpulmonary pressure significantly improves oxygenation, compliance, and minimizes ventilation-induced lung injury.

Keywords: COVID-19, acute respiratory distress syndrome, extracorporeal membrane oxygenation, esophageal balloon.

RESUMEN. El síndrome de insuficiencia respiratoria grave, que no responde a las estrategias convencionales, se beneficia de la terapia de oxigenación por membrana extracorpórea venovenosa. Esta terapia puente se puede complementar con maniobras de ultraprotección pulmonar. La presión transpulmonar puede ayudar a reducir el riesgo de lesión pulmonar inducida por el ventilador debido al atelectrauma. Sin embargo, su beneficio queda por establecerse. Presentamos el caso de un hombre de 34 años con síndrome de insuficiencia respiratoria aguda severa en terapia de oxigenación por membrana extracorpórea venovenosa y ventilación protectora ultrapulmonar, con titulación de presión positiva al final de la espiración por presión transpulmonar. La oxigenación por membrana extracorpórea venovenosa fue decanulada con éxito después de la resolución adecuada del síndrome de insuficiencia respiratoria aguda. En este caso se pudo observar que una estrategia de ventilación que utiliza presiones esofágicas para estimar la presión transpulmonar mejora significativamente la oxigenación, la distensibilidad y minimiza la lesión pulmonar inducida por la ventilación.

Palabras clave: COVID-19, síndrome de dificultad respiratoria aguda, oxigenación por membrana extracorpórea, balón esofágico.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) has a high mortality rate (35-46%).[1,2] Severe ARDS, with PaO_2/FiO_2 of 80 mmHg and no response to conventional mechanical ventilation (MV), requires extracorporeal membrane oxygenation (ECMO) as rescue therapy.[1,3] ECMO therapy provides oxygenation and ventilation,[2] allowing the lungs to rest and recover from respiratory failure while minimizing ventilator-induced lung injury (VILI).[1-3]

Ultraprotective lung ventilation is a strategy that achieves lower airway pressures and tidal volume (TV) than the current standard. This maneuver sets several parameters: low tidal volume (0.5-6 mL/kg/min), high positive end-expiratory pressure (PEEP) (10 to 15 cmH_2O), low plateau pressure (< 25 cmH_2O),[1,2] limited respiratory rate,[2,3] inspiratory time of one to two seconds, low inspiratory pressure (< 15 cmH_2O), and FiO_2 less than 60%.[2,3]

It is feasible to adjust ventilator settings based on transpulmonary pressure (TPP) measurements, which can improve oxygenation and reduce VILI secondary to high pressures and volumes during inspiration and low pressures and volumes during expiration.[1-3] However, there are few studies on ECMO where the impact of PEEP adjustment based on TPP is determined.[3] Transpulmonary pressure measurement is based on esophageal manometry. The aim of this work is to present a case of TPP measurement with

Correspondence:
Venus Nefte López-Zamora, M.D.
Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico City, Mexico.
E-mail: venuslop27@hotmail.com

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esophageal balloon achieving control of VILI in a patient with severe ARDS.

CASE PRESENTATION

A 34-year-old Mexican male with a history of smoking and cocaine abuse, with no history of SARS-CoV-2 vaccination, developed asthenia, hyperthermia and dry cough in February 2022. First treated on an outpatient basis (paracetamol, supplemental oxygen, antibiotics, anticoagulant, steroids, tocilizumab and inhaled bronchodilator), his clinical picture worsened 35 days after symptom onset and he was admitted to the intensive care unit with arterial saturation of 60% and confirmatory COVID-19 test. Advanced airway management was performed, with subsequent recruitment maneuver and PEEP titration for distensibility. However, pulmonary protection goals were not achieved. Due to severe ARDS, the patient was placed in prone position and antibiotic therapy was started due to suspicion of bacterial pneumonia.

Despite pharmacological adjustments (analgesia, sedation and neuromuscular blockade), his poor tolerance to PEEP and persistent refractory hypoxemia (PaO_2/FiO_2 64.9 mmHg), he was considered a candidate for venovenous ECMO (VV ECMO). With SOFA of 10 points, 50% mortality, MuLBSTA score 12 points, 15.99% mortality at 90 days, RESP score six points, risk classification I and hospital survival of 92%. An esophageal balloon was placed and ventilation settings were established with pulmonary ultraprotection. Due to the high requirement for intravenous sedation, inhalation sedation with sevoflurane was administered to achieve deep sedation (bispectral index 34-47) and patient-ventilator synchrony. On day nine, patient-ventilator asynchrony was observed due to secondary false triggering by synglot *(Figure 1)*, so proton pump inhibitors were started and sedoanalgesia was adjusted. On day 17 ECMO support was reduced and MV parameters were adjusted, achieving pulmonary protection goals. Ineffective efforts were determined using esophageal balloon. On day 19 the resolution of ARDS allowed ECMO withdrawal and maintenance of lung protection goals; however, with deterioration 48 hours later due to ventilator-associated pneumonia. A titration procedure with esophageal balloon support and electrical impedance tomography was performed, with adequate resolution at 72 hours. On day 25 rehabilitation was started after removal of neuromuscular blockade and sedation with progressive withdrawal of analgesia. On day 27 tracheostomy was performed, allowing ventilatory progression on day 32, according to TIPS protocol. A positive swallow test was performed on day 42, followed by successful tracheostomy decannulation on day 44 *(Figure 2)*.

DISCUSSION

ARDS has a high mortality rate (35 to 46%).[1,2] Mortality and ventilator days' increase with severity.[2] ARDS is characterized by severely impaired gas exchange. Hypoxemia is mainly due to intrapulmonary shunt, while increased alveolar dead space accounts for impaired CO_2 clearance. Patients with severe ARDS, with PaFi less than 80 mmHg, unresponsive to conventional mechanical ventilation are considered candidates for VV ECMO as rescue therapy.[1,3] The rationale is that extracorporeal

Figure 1:

Hamilton ventilator display showing transpulmonary pressure and esophageal pressure curves with ultra-protection parameters and presence of false trigger secondary to hiccups.

gas exchange allows the use of lung protective ventilator settings, which minimizes VILI.[1-3] While none of the guidelines (REVA, CESAR, ELSO or EOLIA)[2,3] have yet defined the ultra-protection configuration in the ventilator, there is no agreement on its benefit.[1-3] Patients with severe ARDS are more likely to present with VILI. The predominant mechanisms by which VILI occurs include alveolar overdistension (volutrauma), barotrauma, atelectotrauma and inflammation (biotrauma).[1-3] Lung protective ventilation strategies are the current standard of care for patients with ARDS that provide adequate ventilation requirements and minimize VILI. Ultra-lung protective goals include the following settings: low tidal volume (0.5-6 mL/kg/min), high PEEP (10 to 15 cmH_2O), plateau pressure limitation (< 25 cmH_2O),[1,2] limited respiratory rate,[2,3] inspiratory time of one to two seconds, inspiratory pressure < 15 cmH_2O, and FiO_2 below 60%, ideally 30%.[2,3] The optimal strategy for assessing and preventing VILI in ARDS is controversial. In patients with severe ARDS with VV ECMO support the optimal mechanical ventilation strategy is unclear.

Measurement of TPP is based on esophageal manometry. Harmful forces causing alveolar overdistension correlate directly with peak inspiratory TPP, and trauma from recurrent alveolar collapse and reopening correlates with minimal end-expiratory TPP.[4] Therefore, knowledge of end-inspiratory and end-expiratory TPP, rather than just airway pressure, could allow customization of mechanical ventilator settings for each patient to minimize both causes of VILI. The use of the esophageal balloon is an appropriate strategy to assess lung function with a personalized approach.[3]

Grasso *et al.*[5] measured TPP in patients with severe ARDS and increased PEEP until TPP was 25 cmH_2O. Of the patients, 50% responded to increased airway pressure and did not require VV ECMO.

In 2019 Zee *et al.*[6] described eight patients with severe ARDS and indication for VV ECMO, according to the EOLIA trial. They estimated TPP with an esophageal balloon catheter and aimed for a TPP ≤ 25 cmH_2O. The TPP-guided open lung concept resulted in an increased PaO_2/FiO_2 ratio and none of the patients required VV ECMO, with a reduction in mortality of 11%.[6]

In a single-center prospective randomized controlled trial in patients with VV ECMO, 104 patients were randomized to the transpulmonary pressure-guided ventilation or lung rest strategy group.[1] The proportion of patients successfully weaned from VV ECMO in the transpulmonary pressure-guided group was significantly higher than in the lung rest group (71.2 vs 48.0%; p = 0.017).[1]

Limiting tidal volumes to maintain end-inspiratory TPP below 25 cmH_2O has been shown to improve oxygenation and compliance; on the other hand, end-expiratory TPP between 0 and 10 cmH_2O prevents atelectasis.[7] As a strategy to maintain convective ventilation for alveolar nitrogen removal and avoid alveolar collapse during ECMO, a high PEEP level should be combined with a very low tidal volume.[8,9] This stabilizes lung morphology improving lung function and limiting hemodynamic impact.[1,3] However, it is still an uncertain strategy in ECMO.[1] In our patient, adjusting ventilator settings based on transpulmonary pressure measurements by esophageal manometry prevented ventilator-induced lung injury and allowed early identification of asynchrony, which allowed successful weaning from VV ECMO.

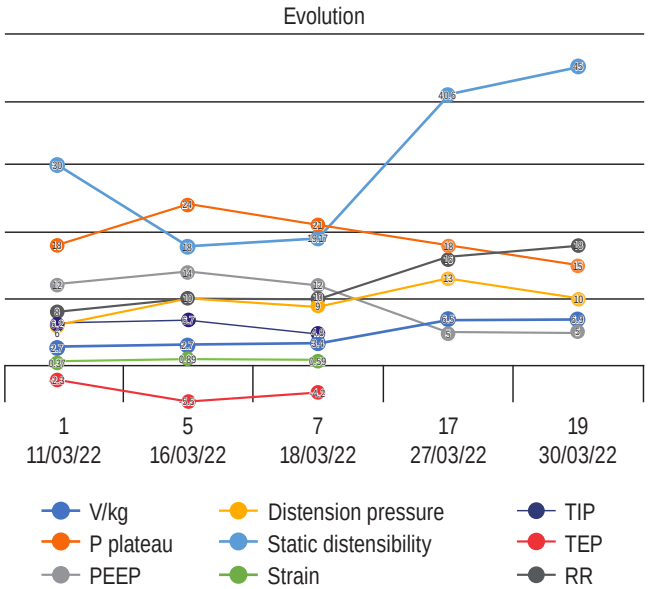

Figure 2: Relevant data on the patient's evolution are presented. Day 27 showed esophageal balloon dysfunction with no possibility of placement due to epistaxis.
PEEP = positive end-expiratory pressure. TIP = transpulmonary inspiratory pressure. TEP = transpulmonary expiratory pressure. RR = respiratory rate.

CONCLUSIONS

A ventilation strategy using esophageal pressures to estimate transpulmonary pressure significantly improves oxygenation, distensibility and minimizes VILI. We present a successful case of a patient with severe ARDS on VV ECMO and transpulmonary pressure monitoring with the use of esophageal balloon catheters that allow finding a PEEP value that could maintain oxygenation, while preventing lung injury due to repeated alveolar collapse or overdistension.

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Clinical case
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Focused transesophageal echocardiography to guide double cannulation in venous-venous ECMO during COVID-19 pandemic

Uso del ecocardiograma transesofágico para la canulación guiada en ECMO venovenosa durante la pandemia del COVID-19

Daniel Manzur-Sandoval,* Edgar García-Cruz,* Daniel Alejandro Navarro-Martínez,* Elisa Mier y Terán-Morales*

*Instituto Nacional de Cardiología «Ignacio Chávez», Mexico City, Mexico.

ABSTRACT. The usage of transesophageal echocardiogram as a guide for positioning cannulas of extracorporeal membrane oxygenation, has become controversial. While extracorporeal membrane oxygenation is largely recommended as a rescue maneuver in patients with COVID-19 who undergo acute respiratory distress syndrome, the usage of transesophageal echocardiogram is not recommended by the American Society of Echocardiography due to the high transmission rate from this pathogen. However, transthoracic echocardiogram has important limitations in patients with acute respiratory distress syndrome that make transesophageal echocardiogram necessary under such circumstances. In this case report, we review the case of a 38-year-old male with severe acute respiratory distress syndrome due to COVID-19 that was started on venous-venous extracorporeal membrane oxygenation. We also describe how the extracorporeal membrane oxygenation team of our institution performs a low-risk focused transesophageal echocardiogram-guided venous-venous extracorporeal membrane oxygenation cannulation adapting to the World Health Organization recommendations on personal protective equipment and the Extracorporeal Life Support Organization recommendations on extracorporeal membrane oxygenation cannulation.

Keywords: extracorporeal membrane oxygenation, transesophageal echocardiogram, COVID-19, cannulation, acute respiratory distress syndrome.

RESUMEN. El uso del ecocardiograma transesofágico como guía para la colocación de cánulas en la oxigenación por membrana extracorpórea ha sido controversial. Mientras que la oxigenación por membrana extracorpórea es ampliamente recomendada como una técnica de rescate en pacientes con COVID-19 que desarrollan síndrome de dificultad respiratoria aguda (SDRA), el uso del ecocardiograma transesofágico no está recomendado por la Sociedad Americana de Ecocardiografía debido al riesgo de contagio elevado de este patógeno. No obstante, el ecocardiograma transtorácico tiene limitaciones importantes en pacientes con SDRA, lo que hace que el ecocardiograma transesofágico se convierta en una necesidad bajo estas circunstancias. En este reporte hacemos una revisión de un paciente masculino de 38 años con diagnóstico de SDRA, grave secundario a infección por COVID-19, en el cual se inició asistencia con oxigenación por membrana extracorpórea venovenosa. También, describimos cómo el equipo de la oxigenación por membrana extracorpórea en nuestra institución realiza la canulación por medio de ecocardiograma transesofágico manejando el menor riesgo posible y adaptándose a las recomendaciones de la Organización Mundial de la Salud acerca del equipo de protección personal y las recomendaciones de las guías de *Extracorporeal Life Support Organization*.

Palabras clave: oxigenación por membrana extracorpórea, ecocardiograma transesofágico, COVID-19, canulación, síndrome de dificultad respiratoria aguda.

Correspondence:
Daniel Alejandro Navarro-Martínez, M.D.
Instituto Nacional de Cardiología «Ignacio Chávez», Mexico City, Mexico.
E-mail: navarro.daniel@uabc.edu.mx

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INTRODUCTION

More than two years have passed since the onset of the COVID-19 disease outbreak. At this point in the pandemic, the number of critically ill patients is declining; however, information about diagnostic protocols and management remains scarce.

An example of this deficiency is the controversial use of transesophageal echocardiography (TEE) in critically ill patients with COVID-19 to guide extracorporeal membrane

oxygenation (ECMO) cannulation. Undoubtedly, TEE is a support tool for intensivists to be able to set management goals within the intensive care unit. Furthermore, it has been shown to be the ideal modality for patients with COVID-19 who are hemodynamically unstable or who require serial pulmonary assessments, support during cardiac arrest resuscitation, and guidance during venous-venous extracorporeal membrane oxygenation (VV ECMO) cannulation.[1] However, some societies such as the American Society of Echocardiography have mentioned that despite the usefulness of TEE in the management and evaluation of critically ill patients with COVID-19, this imaging modality represents an increased risk of viral transmission. This is why the use of TEE should be considered with caution.[2]

At the Instituto Nacional de Cardiología «Ignacio Chávez» in Mexico City, TEE is preferred over transthoracic echocardiography (TTE) for VV ECMO cannulation. During the last year, a case series of 13 patients in which TEE was used to guide successful VV ECMO cannulation was published.[3]

In this case report we explain the protocol that intensive care physicians at the institute follow during TEE-guided placement of extracorporeal membrane oxygenation cannulae.

CASE PRESENTATION

A 38-year-old man with acute respiratory distress syndrome (ARDS) secondary to COVID-19 infection refractory to conventional treatment and ventilation in the prone position, for which ventricular support with VV ECMO was initiated. This was done following the protocol and recommendations of the World Health Organization (WHO) regarding personal protective equipment (PPE) and adapting the recommendations for TEE-guided ECMO cannulation of the Extracorporeal Life Support Organization (ELSO).[4] Based on this, the ECMO team was composed of intensivists specialized in critical echocardiography trained with the skills to guide real-time ECMO cannulation in order to limit microdroplet exposure time and, likewise, ECMO-associated complications such as bleeding, infection, malpositioning and recirculation.

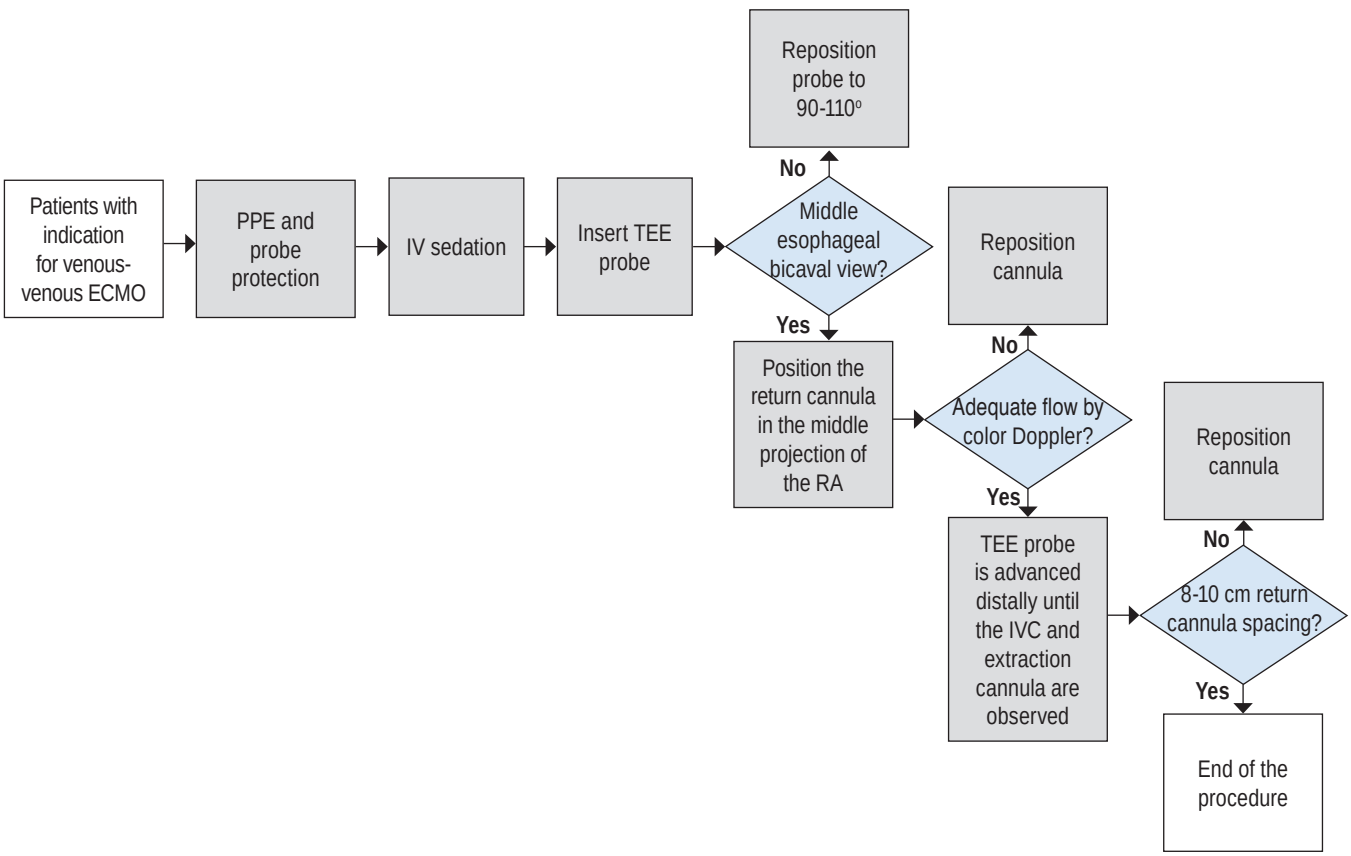

Figure 1: Flowchart of transesophageal echocardiogram use during venovenous extracorporeal membrane oxygenation cannulation.
ECMO = extracorporeal membrane oxygenation cannulation. PPE = personal protective equipment. TEE = transesophageal echocardiogram. RA = right atrium. IVC = inferior vena cava. VV ECMO = venous-venous extracorporeal membrane oxygenation cannulation.

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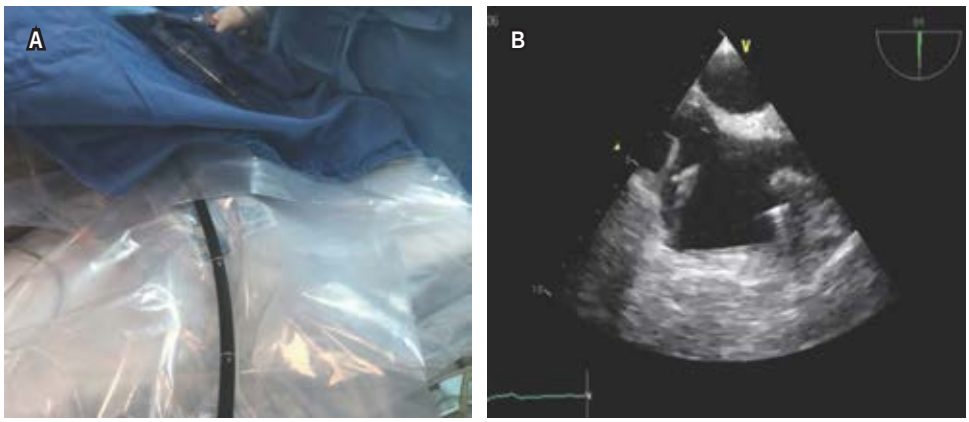

Figure 2:

A) Transesophageal echocardiography probe covered with a plastic layer. **B)** Midesophageal bicaval 90-110º projection where we observe right atrium, superior and inferior vena cava.

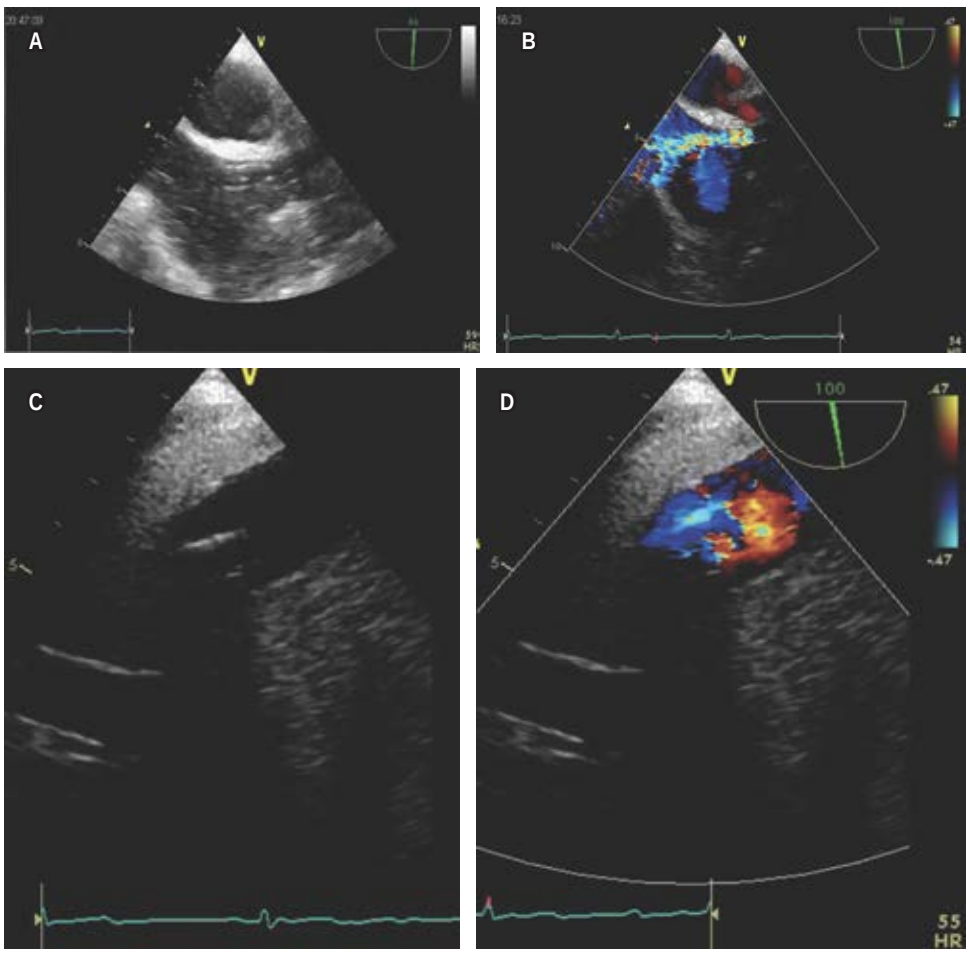

Figure 3:

A) 90-110º bicaval mid esophagus where we observe the return cannula (jugular) in the middle segment of the right atrium. **B)** Same image with color Doppler. **C)** Bicaval mid esophageal bicaval projection distal 90-11º where we observe the inferior vena cava with the extraction cannula (femoral). **D)** Same image with color Doppler.

As the first step of the flowchart *(Figure 1)*, all personnel must have adequate PPE and protect the TEE probe *(Figure 2A)*. After intravenous sedation, the TEE probe is inserted, being the projection selected to guide the procedure the mid esophageal bicaval 90-110 degree view *(Figure 2B)*, where we can guide in real time the correct positioning of the return (jugular) cannula *(Figure 3A)*, which should be placed in the mid portion of the right atrium in the direction of the tricuspid valve. Adequate flow can be assessed by color Doppler *(Figure 3B)*. The TEE probe with the same degree of angulation is advanced distally toward the esophagus to observe the inferior vena cava and the extraction cannula (femoral) which should be separated 8 to 10 cm from the return

cannula *(Figure 3C and D)*; this limits suction and recirculation phenomena.

DISCUSSION

The ELSO, WHO and the Surviving Sepsis Campaign Guidelines recommend considering ECMO in specialized centers as a rescue maneuver in patients with COVID-19, acute respiratory distress syndrome and severe hypoxemia despite optimal medical treatment.[5] The reported hospital mortality in patients with COVID-19 receiving ECMO is 37.1%.[6] Given the high rate of transmission of this pathogen through airborne particles, societies such as the American Society of Echocardiography[2] do not recommend some procedures such as transesophageal echocardiography as a first diagnostic approach. The ELSO group suggests that VV ECMO and cannulation should be guided by TEE to ensure correct positioning of the cannulae.[4] On the other hand, in cases where there is biventricular dysfunction, the use of VV ECMO will be insufficient to improve the patient's clinical condition. These patients can be adequately selected by TTE; in addition, there are reports of the use of TTE as a tool to guide VV ECMO cannulation;[7] however, patients with ARDS often have a poor acoustic window due to positive pressure during mechanical ventilation, prone decubitus and/or obesity, so image quality is not always optimal; TEE is necessary in these scenarios.

CONCLUSIONS

Severe forms of COVID-19 infection will continue to be a frequent scenario in intensive care units in the coming years, making the integration of multidisciplinary teams capable of providing mechanical respiratory and circulatory support mandatory. Therefore, any imaging evaluation should be done in a «focused» manner to minimize staff exposure to infectious particles, while providing the best evidence-based management of critically ill patients.

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Malignant fibrous histiocytoma, case report

Histiocitoma fibroso maligno, reporte de caso

Juan Carlos Martínez-Osorio,* Manuel Antonio Escalera-Bustamante,*
Luis Ortiz-Cordero,* Emmanuel Escobedo-Sánchez*

*Centro Médico, Instituto de Seguridad Social del Estado de México y Municipios. Toluca, Mexico.

ABSTRACT. The term malignant fibrous histiocytoma was introduced by O'Brien and Stout for tumors of fibrocystic lineage. Malignant fibrous histiocytoma is the second most common soft tissue sarcoma of the musculoskeletal system after liposarcoma. The treatment of choice is surgery with wide resection margins, with radiotherapy and chemotherapy being complementary treatments to surgery. Study of a 68-year-old female patient in a Thoracic Surgery Service. Patient with malignant fibrous histiocytoma, observation and detailed description of the patient's clinical history, evolution of the disease, treatment and results obtained in the patient. Risk factors, such as exposure to biomass. Multidisciplinary management allows a timely approach and benefit in the result of long-term treatment for the patient. The use of the VAC system and thoracoscopy, to work together in the surgical approach, allow the reduction of wound healing and closure time, together with a reduction in the days of hospital stay, while also reducing hospital costs inherent to these pathologies.

Keywords: case report, thorax surgery, plastic surgery, VAC system, malignant fibrous histiocytoma.

RESUMEN. El término histiocitoma fibroso maligno fue introducido por O'Brien y Stout para tumores de linaje fibroquístico. El histiocitoma fibroso maligno es en nuestro medio el segundo sarcoma de partes blandas más frecuente del sistema musculoesquelético después del liposarcoma. El tratamiento de elección es la cirugía con márgenes de resección amplios, siendo la radioterapia y quimioterapia tratamientos complementarios de la cirugía. Estudio de tipo observacional que presenta detalladamente el reporte de un caso de paciente femenino de 68 años en un servicio de cirugía de tórax. Paciente con histiocitoma fibroso maligno, observación y descripción detallada sobre historia clínica, evolución de la enfermedad, tratamiento y resultados obtenidos en la paciente. Factores de riesgo como la exposición a biomasas que propiciaron esta condición de forma crónica. El manejo multidisciplinario permite un abordaje oportuno y beneficioso en el resultado del tratamiento a largo plazo para la paciente. El uso del sistema VAC y la toracoscopia para un trabajo en conjunto en el abordaje quirúrgico permiten la reducción del tiempo de cicatrización y cierre de heridas, en conjunto a una reducción en los días de estancia intrahospitalaria, mientras que también reduce costos hospitalarios inherentes a estas patologías.

Palabras clave: reporte de caso, cirugía de tórax, cirugía plástica, sistema VAC, histiocitoma fibroso maligno.

INTRODUCTION

Malignant fibrous histiocytoma is the most common soft tissue tumor in adults, the term was first introduced in 1963. O'Brien and Stout introduced the term malignant fibrous histiocytoma for tumors of fibrocystic lineage. Weiss and Enzinger described myxoid malignant fibrous histiocytoma, which shares several features with myxofibrosarcoma; and classified it into grades, according to its histology: low grade (myxoid predominant), intermediate grade (mixed: myxoid and cellular) and high grade (predominantly cellular).[1] However, in 2002 the World Health Organization classified malignant fibrous histiocytoma as an entity and determined that the myxoid type without myogenic, lipoblastic and chondrogenic factors is classified as myxofibrosarcoma.[2]

Malignant fibrous histiocytoma is the second most frequent soft tissue sarcoma of the musculoskeletal system after liposarcoma. It arises from pluripotential mesenchymal

Correspondence:
Juan Carlos Martínez-Osorio
Instituto para el Desarrollo Académico de Estudiantes de Excelencia en Medicina, A.C.
E-mail: juancm10@ucm.es

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cells capable of differentiating from histiocytes, fibroblasts and myofibroblasts found in connective tissue.[3]

Macroscopically, malignant fibrous histiocytoma appears as a large tumor with multiple areas of necrosis on the cut surface. Microscopically the tumor shows a disorderly proliferation of spindle cells with occasional stellate or swirling pattern, presence of multinucleated cells with large nuclear atypia, bizarre shapes, frequent atypical mitosis figures, and a stroma showing a large amount of collagen, as well as a variable number of mononucleated inflammatory cells and foamy histiocytes. Its diagnosis is clinical and paraclinical. Cruz states that in 74% of cases it is made on the basis of macroscopic and microscopic morphology, but even so he recommends the use of immunohistochemistry, which is considered fundamental by Miettinen because of the heterogeneity of these lesions.[4]

Multidisciplinary treatment is essential for two reasons: 1) because the prognosis of these neoplasms is determined by the histological grade and size of the tumor; and 2) because up to 22% of cases present clinical metastatic disease from the outset.[4]

CASE PRESENTATION

Female patient aged 68 years with primary school education, originally from Guanajuato, occupation: flower trader and exposure to fertilizers for 11 years. Allergies to contrast medium, allergy to drugs: trimethoprim-sulfamethoxazole, omeprazole, gentamicin and metamizole.

Diagnosed with type 2 diabetes mellitus for 11 years, on treatment with metformin 850 mg every 24 hours and insulin lispro 50 IU in the morning and 30 IU at night every 24 hours. History of systemic arterial hypertension in treatment with losartan 50 mg every 12 hours, since 11 years ago. Diabetic neuropathy in treatment with pregabalin 75 mg every 24 hours for the last five years.

Surgical history: a cesarean section 32 years ago without complications, a laparoscopic fundoplication in 2001 secondary to gastroesophageal reflux disease without complications, a total abdominal hysterectomy secondary to uterine myomatosis 15 years ago with need for blood transfusion (type and amount of blood products transfused are unknown). A laparotomy for intestinal occlusion 15 years ago without complications and an open cholecystectomy 13 years ago, without complications.

She started her current condition in November 2021 with pain in the left hemithorax and shoulder, pulsating, with intensity 5/10 VAS (visual analog scale), intermittent, accompanied by weight loss of 5 kg in the last month, fever and nocturnal diaphoresis. She consulted a physician and received multiple treatment with non-steroidal anti-inflammatory drugs (NSAIDs), without improvement.

From day one of hospital stay, she started with antibiotic therapy with ceftriaxone 1 g every eight hours, her control medications metformin, losartan and insulin lispro. On her fourth day analgesia with paracetamol and ketorolac was added, as she began to report pain of intensity 6/10 VAS.

On his fifth day of in-hospital stay he presented dyspnea and hypertensive crisis, enoxaparin 60 mg every 24 hours, nifedipine 30 mg every 24 hours and oxygen with nasal prongs 3 L × min were added to his treatment regimen.

On his seventh day of stay, he underwent radiography of the shoulder and left arm, with no abnormal radiological data, only with increased volume in the soft tissues of the left arm. An axial, coronal and sagittal computerized tomography was also performed, showing a hypodense area at the level of the left costoclavicular joint, and a central venous catheter was placed.

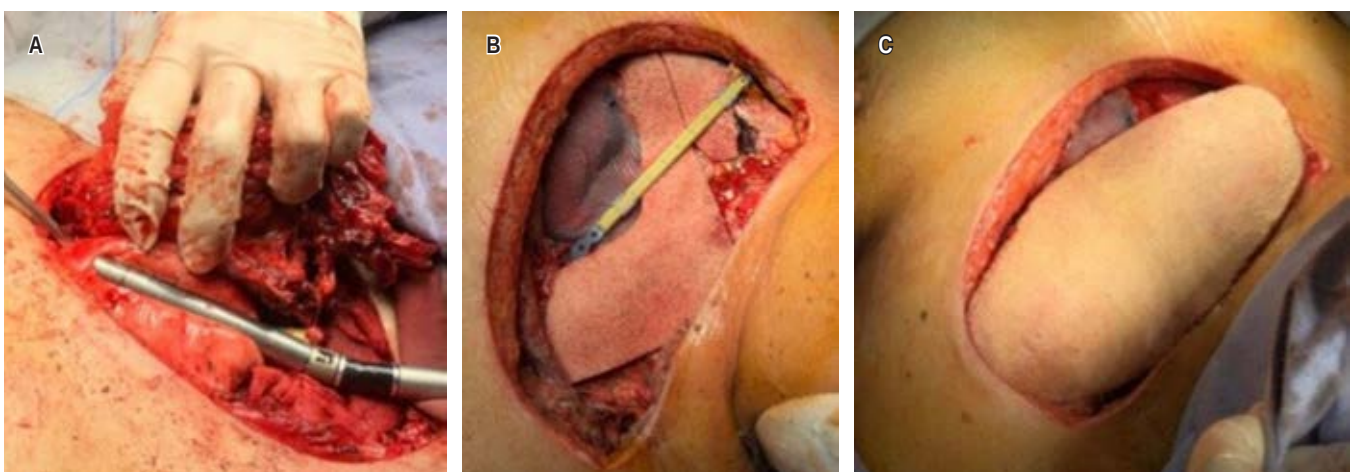

Figure 1: A) Tumor resection with linear stapler, lung segment is taken. **B)** Titanium prosthesis that maintains the structure of the thoracic cage in resection sites. **C)** Pedicled latissimus dorsi and skin flap at the resection site.

Figure 2:

A) Resected tumor with free borders of approximately 16 cm in its longitudinal axis. **B)** Resected tumor with lateral view of its layers, from inferior to superior, skin and subcutaneous tissue, pectoral muscles, costal arches, lung. **C)** X-ray of tumor with presence of calcification in layer in all its morphology. **D)** Flap two weeks after surgery, peripheral necrosis towards medial thorax.

On the tenth day of her stay, she received a consultation from the psychology department, which showed improvement in her mood. On this day she was admitted to the operating room, and on 03/24/2022 a malignant tumor of the thorax was excised. Surgical findings showed an 8 cm diameter tumor in the anterior sternal face and left hemithorax with undefined borders, indurated, fixed to deep planes, with fatty infiltration, erythematous changes and presence of erosion at cutaneous level, with left pleuropulmonary invasion in the upper lobe, very friable tissue of petrous consistency, without invasion of vessels.

Technique: a spindle incision is made at the level of the anterior wall leaving a 4 cm border peripheral to the lesion and block resection is performed with exeresis of the left clavicle, first and second ribs, as well as partial sternotomy of the manubrium and upper third of the sternal body to the cartilage of the first and second right costal arches, as well as the clavicular union, identifying without invasion of the subclavian vein and artery, innominate vein and large vessels. Non-anatomic resection of the anterior wall of the upper pulmonary lobe infiltrated by tumor was performed with a stapler, with no evidence of leakage *(Figure 1A)*. Hemostasis was verified and DualMesh was placed in the pleuropulmonary resection site, as well as StraTos system bar placement in the second costal arch, bilaterally *(Figure 1B)*. White sponge is placed to cover large vessels and then VAC system (vacuum-assisted closure) is placed with gray sponge at a continuous suction of 50 mmHg, left endopleural probe is placed under direct vision with thoracoscope, seal is placed with continuous suction at 20 cm^3.

Plastic surgery (25/03/2022): incision on previously marked cutaneous island at the level of the left lumbar region, 19 × 9 cm, spindle-shaped, cutting dissection is performed until reaching the aponeurosis of the latissimus dorsi to its anatomical limits, disinsertion of the latissimus dorsi muscle from lateral, medial and inferior end is performed, disinserting the muscle with superior pedicle up to 3 cm below the axillary hollow. Hemostasis is verified. Biovac drainage is placed in the left lumbar region. A suprafascial tunnel was made at the left axillary level towards the cruciate area in the anterior hemithorax measuring 19 × 9 cm. Wound plane closure was performed on the dorsum, SCT (subcutaneous cellular tissue) with 2-0 vicryl inverted in deep plane, 3-0 vicryl in dermis and skin with staples. BIOVAC type drainage is fixed with 3-0 nylon. The patient is placed in dorsal decubitus and the VAC system is removed, gray sponges and white sponge are removed, showing bone exposure with loss of clavicular segments and first and second ribs resected in the previous procedure with StraTos system bar in bilateral second costal arch, pulmonary exposure with DualMesh, exposure of great vessels, pectoralis major segments and adjacent nerves. We proceed to externalize the previously tunneled flap and fix the wide dorsal flap to the deep tissue, place the cutaneous island in its final position *(Figure 1C)*, place a superolateral Penrose drain and another inferolateral Penrose drain. After hemostasis, closure is performed by planes, 2-0

vicryl inverted stitches for SCT and then 3-0 vicryl inverted stitches, the skin is faced with cardinal staples.

The surgical specimen is shown with respected edges *(Figure 2A and B)*, of which radiography is taken *(Figure 2C)*. Follow-up image is shown two weeks after surgery *(Figure 2D)*.

DISCUSSION

Secondary to a multidisciplinary management between surgical services such as thoracic surgery (resection) and plastic and reconstructive surgery (reconstruction), it was possible to obtain beneficial results and survival for the patient, and the patient has been continuously followed up by both services until today.

CONCLUSION

Multidisciplinary management is of utmost importance to ensure the patient's well-being. The joint management allowed a timely and beneficial approach in the outcome of long-term treatment for the patient. The use of the VAC system and thoracoscopy to work together in the surgical approach allows a reduction of the healing time and wound closure, a shortening of the days of hospital stay and also a reduction of hospital costs inherent to these pathologies.

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Mediastinal liposarcoma in an adolescent

Liposarcoma mediastinal en una adolescente

Juliana Lucia Molina-Valencia,* Walter Romero-Espitia,‡ Angelo Loockhart‡

*Universidad de Antioquia, Medellín, Colombia; ‡Hospital San Vicente Fundación, Medellín, Colombia.

ABSTRACT. Sarcomas of the mediastinum are rare. The incidence in pediatric age is unknown. Its symptoms are caused by the compression of structures in the mediastinum. We present a case of a 15-year-old adolescent, she had dyspnea and chest pain, an anterior mediastinal mass was identified, in imaging studies the mass had various areas of soft tissue density and fatty tissue with histology reporting liposarcoma. She was managed with surgical resection and postoperative radiotherapy. Less than 25 cases have been reported in children under 18 years of age, surgical management is the mainstay in treatment and the prognosis is given by complete resection of the lesion.

Keywords: neoplasms, mediastinum, sarcoma, surgery.

RESUMEN. Los sarcomas del mediastino son raros. Se desconoce la incidencia en la edad pediátrica. Sus síntomas son causados por la compresión de estructuras en el mediastino. Presentamos el caso de una adolescente de 15 años con disnea y dolor torácico, se identificó una masa en mediastino anterior, en estudios imagenológicos la masa presentaba diversas áreas de densidad de tejidos blandos y tejido graso con histología que reportó liposarcoma. Se manejó con resección quirúrgica y radioterapia posoperatoria. Se han reportado menos de 25 casos en menores de 18 años, el manejo quirúrgico es el pilar del tratamiento y el pronóstico está dado por la resección completa de la lesión.

Palabras clave: neoplasias, mediastino, sarcoma, cirugía.

INTRODUCTION

The laxity of the tissues that delimit the mediastinum allows to harbor large tumors before generating symptoms by compressing neighboring structures such as the tracheobronchial tree, vascular structures and esophagus, producing dyspnea, dysphonia, chest pain and dysphagia. The most common neoplasms of the mediastinum in children are lymphoma, neurogenic tumors, and germ cell tumors. In both asymptomatic and symptomatic patients with mediastinal masses, imaging studies that identify the location to the anterior, middle, or posterior mediastinum will be essential for the initial diagnostic approach.[1]

Soft tissue sarcomas are rare malignant tumors, representing less than 1% of all malignant neoplasms and specifically in the thorax less than 0.01%. Mediastinal sarcoma accounts for less than 10% of mediastinal tumors and is usually metastatic from sarcomas originating in the extremities, retroperitoneum, head, and neck.[2]

The average age of diagnosis of sarcomas in the mediastinum is 40 to 50 years, the prevalence in pediatric age is not exactly known due to its infrequency. 70% are spontaneous onset, 13% have a history of radiation to the chest and mediastinum, and 10% have associated hereditary syndromes, such as Li-Fraumeni, Gardner's syndrome, retinoblastoma, and neurofibromatosis (Von Recklinhausen's disease).[3] Liposarcoma is the most common histological type in the anterior mediastinum, but there are limited data on differences in clinical presentation and treatment outcome between adult and pediatric patients. The objective of this work is to present a case of mediastinal liposarcoma in a pediatric patient.

CASE REPORT

A 15-year-old adolescent with a history of cutaneous lupus was admitted with a five-month evolution of asthenia, adynamia, dyspnea on medium efforts and pleuritic chest pain in the right hemithorax, without B symptom. In the study of dyspnea, a contrasted chest computed tomography (CT) was performed: anterior mediastinal mass of 124 × 90 × 87 mm with various areas of soft tissue density and fatty tissue elements, extending posteriorly until compromising the mediastinal fat of the junction between the superior mediastinum and inferior, in contact, without infiltrating the

Correspondence:
Juliana Lucia Molina-Valencia, MD
Universidad de Antioquia.
E-mail: juli.moli@hotmail.com

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walls of the left venous brachiocephalic trunk, the arch of the azygos vein, the right brachiocephalic artery, the dorsal and middle ventral aspect of the superior vena cava as well as the ventral aspect of the ascending segment of the aorta a level of the arch and the right anterior and medial aspect of the pulmonary artery infundibulum and exerting extrinsic compression without infiltration of the wall at the level of the right atrium, without evidence of metastatic lesions *(Figure 1)*. A biopsy was performed by mediastinoscopy that reports myxoid liposarcoma without a round cell component.

She is taken to surgery for resection of the mass with a sternotomy approach where a solid tumor is identified, lobulated 10.5 × 7.5 × 6.0 cm of yellow and orange color that extended to the anterosuperior and middle mediastinum, firmly adhered to the right pleura, medial mediastinal tract, involving the left venous brachiocephalic trunk, right subclavian vein, superior cava in contact with the anterior and lateral wall of the trachea and around the right main bronchus, without evidence of pulmonary or pleural metastases, no pleural effusion, or mediastinal lymphadenopathy, with adequate plane of separation of the pericardium. Complete resection is achieved macroscopically by resecting the thymus *(Figure 2)*. The surgical bed is marked with titanium clips. Right and left mediastinal drainage catheter was left.

Adequate postoperative evolution, she was extubated and transferred to the ICU for surveillance, analgesic management with opioid, control radiography with adequate position of chest drainage and pulmonary expansion, without the need for transfusion support or vasopressor. On the fourth day she was discharged.

Pathology report: neoplasm composed of adipose tissue with abundant type II and multivacuolated lipoblasts with hyperchromatic nucleolus with less than one mitosis per field distributed in myxoid stroma with spindle cells with minimal atypia which are accompanied by curvilinear vessels. Fragments of lymph node and brown fat can be seen on one side. Immunohistochemical studies are performed S100, CK, CDK4, AML negative, Desmin negative, CD34 positive, p16 focally positive, Ki67 8%. Suggests myxoid liposarcoma without round cell component, mitosis up to 1 × 10 high power fields. Histological grade I, negative margins for compromise, unidentified lymphovascular invasion, no compromised lymph nodes identified.

Patient with stage IB T3N0M0 liposarcoma grade I, R0 resection. Postoperative radiotherapy was offered at a dose of 45 in 1.8 Gy fractions (anterior mediastinum). Follow-up at the institution with chest contrasted tomography every six months, last control was in December 2020, the patient was asymptomatic and without evidence of relapse in images.

DISCUSSION

Mediastinal sarcomas are very uncommon in pediatric age, the most common soft tissue sarcoma is malignant fibrous hyosthiocytoma (24%), followed by liposarcoma (14%).[4]

Figure 2: Mediastinal mass after surgical resection.

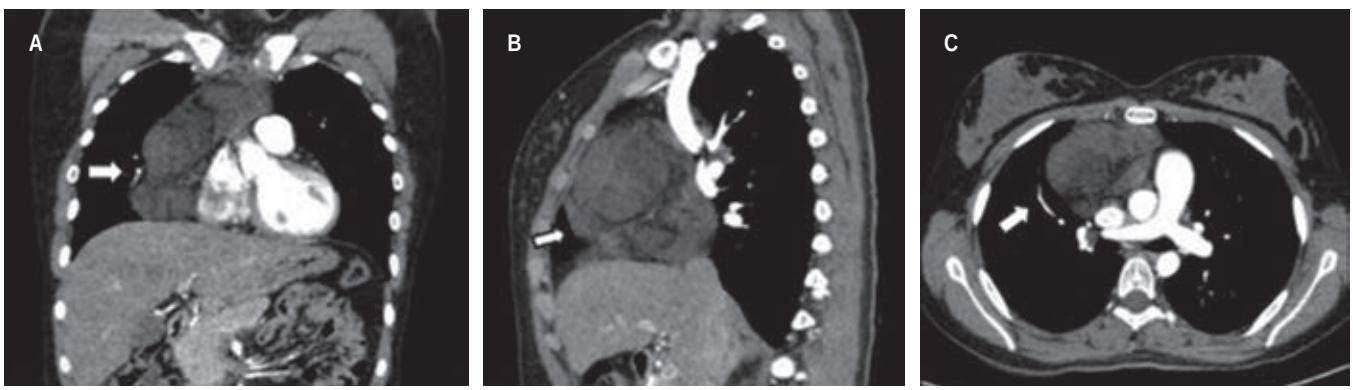

Figure 1: Contrast-enhanced chest computed tomography. Arrow points the mass in anterior mediastinum. **A)** Coronal plane, **B)** sagittal plane, **C)** axial plane.

Table 1: Liposarcoma cases reported in patients under 18 years.

Author (year)	Age/sex	Location	Treatment	Recurrence	Follow-up
Perkins (1939)	18/F	Posterior	Surgery	–	Alive 3 years
Joske (1944)	18/M	Posterior	Surgery	–	–
Kauffman (1959)	2/F	Superior	Surgery	2 years	Alive 4 years
Wilson (1964)	1/F	Anterior	Surgery	–	Alive 8 months
Cicciarelli (1964)	13/F	Right thorax	Surgery + radiotherapy	9 months	Died 2 years
Cicciarelli (1964)	15/F	Posterior	2 Surgery's	Yes	–
Aldor (1979)	12/M	–	Surgery	–	–
Castelberry (1984)	14/M	Anterior	Chemo/radiotherapy+ surgery	–	Alive 14 months
Koster (1985)	14/M	–	Surgery	–	–
Plucker (1988)	5/M	Anterior	Surgery + chemotherapy + surgery	10 months	Died 7 months
La Quaglia (1993)	18/M	Posterior	Surgery + chemotherapy + brachytherapy	–	Died
Mikkilineni (1994)	17/M	Posterior	Surgery + chemotherapy	9 months	Died 9 months
Klimstra (1995)	14/-	Anterior	–	–	–
Klimstra (1995)	< 18/-	–	–	–	–
Chiyo (2001)	13/F	Anterior	Surgery	–	Alive 35 months
Tian (2002)	12/M	Left anterior superior	Surgery	–	Died 5 months
Hahn (2007)	14/F	Posterior	Surgery	No	Alive 53 months
Hahn (2007)	3/M	Anterior	Surgery	No	Alive 36 months
Hahn (2007)	7/F	–	Surgery	–	–
Rajan (2010)	11/F	Posterior superior	Surgery	No	Alive 20 months
Saeed (2010)	17/F	Anterior	Surgery + chemo/radiotherapy	–	–
Chen (2014)	16/F	–	Surgery	No	Alive 36 months
Zheng (2021)	14/F	Left thorax	Surgery	–	–
Romero (present case)	15/F	Right anterior superior	Surgery + radiotherapy	No	3 years

M = masculine. F = female.
Modified from: Anand Rajan KD, *et al*.[6]

Primary intrathoracic liposarcoma only represents 0.1 to 0.75% of all mediastinal tumors, it does not have a predisposition based on sex, and the diagnosis is more frequent in those over 40 years of age.[5] Less than 25 cases have been reported in children under 18 years since 1939 *(Table 1)*, with more frequent locations in the anterior and posterior wall of the thorax, all of them undergoing surgical management.[6]

Mediastinal liposarcomas can present with rapid growth leading to compression of adjacent structures with typical symptoms such as those presented by the patient. Dyspnea, tachypnea and chest pain, are the most common symptoms, but non-specific, which is why there is a delay in the diagnosis, as in the reported patient who had been experiencing these symptoms for five months. Dysphonia, superior vena cava syndrome, wheezing, arrhythmias and heart failure have been described; 85% of patients have symptoms and 15% are incidental imaging findings.[5,7] When the growth is massive, a distinctive clinical entity known as «giant mediastinal liposarcomas» appears, a term that should be used as proposed by Nguyen et al, when the liposarcoma reaches a size greater than 10 cm and is associated with compressive symptoms.[5]

Histologically, liposarcoma is divided into four large subtypes: well differentiated, myxoid/round cells, dedifferentiated and pleomorphic; 40% to 50% are myxoid liposarcomas as in the

reported case. The histological types are correlated with the potential for metastasis, this subtype being the least aggressive and the pleomorphic one having the worst prognosis.[4,8]

Depending on the degree of differentiation, in the tomography, a mass of fatty tissue with a variable soft tissue component may be evidenced, however these characteristics are not sufficient for diagnosis and a histological study is always required. Various techniques have been used for biopsy of mediastinal masses, ultrasound or tomography-guided biopsy, mediastinoscopy, mediastinotomy and open surgery.[9] The most used are image-guided and the decision for that choice is based on tumor size, location and the clinical characteristics of the patient, as reported by Tanaka et al that in order to evaluate safe diagnostic strategies for pediatric patients with respiratory distress caused by mediastinal tumors, they analyzed the records of 12 patients and report different strategies as cytology and flow cytometry of the pleural effusion, if present, core needle biopsy under local anesthesia and tumor markers.[7]

An R0 (macroscopic and microscopic negative margins) resection is the main independent prognostic factor for disease-free survival and overall survival.[3] If the liposarcoma is small, minimally invasive approaches can be considered. The usual management is resection by open surgery, depending on the location the approach can be by sternotomy, anterolateral or posterolateral thoracotomy, clamshell.[3] In the cases reported in adults by Jimenez *et al*, the approach of choice was posterolateral thoracotomy; in our patient, due to the location of the lesion, the best exposure was achieved with a sternotomy. To carry out a complete resection, 34% of cases require resection with reconstruction of larger structures.[3]

Postoperative radiation therapy is considered the ideal management for almost all intermediate-grade and high-grade soft tissue sarcomas. The recommended radiation dose is 60-66 Gy in fractions of 1.8-2 Gy. Local recurrence develops in approximately 13% of patients with 5-year, 10-year, and 15-year survival rates after surgery and radiation therapy of 79, 69, and 61%, respectively.[10] The patient in the present case in a 3-year follow-up after treatment with radiotherapy has not presented relapse.

CONCLUSION

Mediastinal liposarcoma is a rare entity and more so in the pediatric population, usually at the time of its presentation they are large tumors that require open surgical approaches and the need for resection of infiltrated adjacent structures. The main prognostic factor for disease-free survival is an R0 resection, for which surgical planning and interdisciplinary management are essential for the management of these patients.

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Richard W Light MD, *in memoriam*. One year after his departure

Dr. Richard W Light, *in memoriam*. A un año de su partida

José Luis Sandoval-Gutiérrez*

*Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico City, Mexico.

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In mid-May 2021 we became aware of the death of one of the most prestigious physicians in respiratory health.

Dr. Light *(Figure 1)* achieved worldwide fame with his classic article on pleural pathology[1] with a large clinical component that decades later is still useful for the medical approach to this entity.

He was always a great guest of our medical society, which he gladly attended with his wife Judi on many occasions. He forged great friendships with several colleagues, he was always cheerful and willing to take many pictures with all those who asked him, especially those in the process of training.

He discussed in his articles the five keys to professional success:

1. Be persistent.
2. Be organized.
3. Look for win-win situations.
4. Adapt to the environment.
5. Finally, and most importantly, sleep every night with the right person for your life.[2]

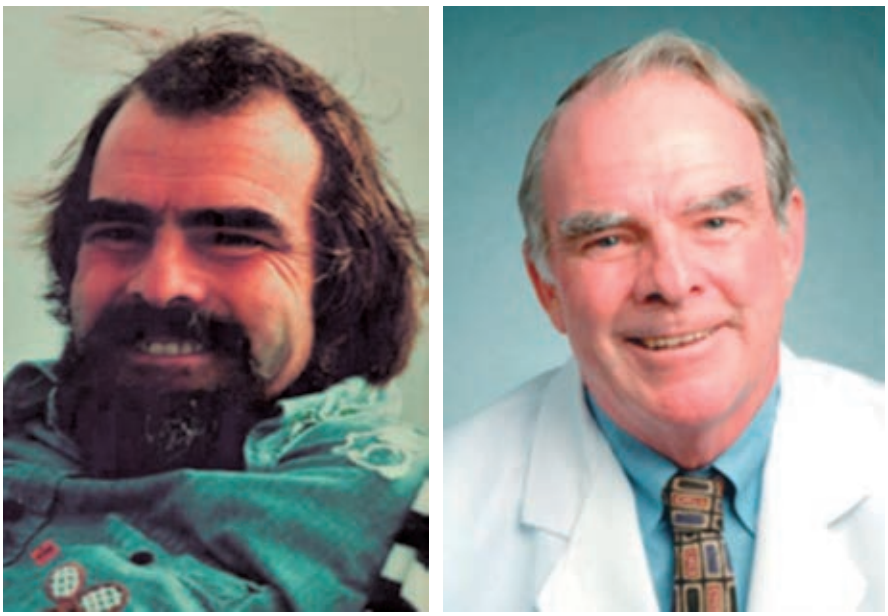

Figure 1: Dr. Richard Light through time. Available in: https://pubmed.ncbi.nlm.nih.gov/25367468/

Like all excellent minds, they are not only great teachers of science, but also of life, we will follow their teachings for the benefit of patients and our lives.

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Correspondence:
José Luis Sandoval-Gutiérrez, M.D.
Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas.
Mexico City, Mexico.
E-mail: sandovalgutierrez@gmail.com

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