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3D TOMOGRAPHIC RECONSTRUCTION OF TWO COVID-19 CASES WITH DIFFERENT RT-PCR RESULTS AND THEIR CLINICAL PICTURE: A COMPARATIVE CASE STUDY

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ABSTRACT

This study compared CT images by 3D processing two RT-PCR negative and positive patients respectively, to investigate the contribution of CT scans in the diagnosis of COVID-19. Two patients were blindly selected and paired for sex, age, outcome and hospitalization time, in addition to the presence of RT-PCR and CT scans of the chest on admission. For the creation of the 3D model, the free software 3D Slicer was used, based on images in the DICOM format. The image patterns identified in the chest CT scans of both patients are similar to the findings described in the literature, namely multiple ground-glass opacities (GGO), lobular, bilateral with peripheral distribution, these being typical characteristics of CT scans resulting from viral pneumonia, properties which, in the context of the pandemic, are associated with COVID-19. The results obtained do not allow to affirm that there is a direct relationship between the affected pulmonary regions and their extension, and the result of the RT-PCR, however, point to the need of triangulating sources of information to support the diagnosis of this yet fully known syndrome.

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INTRODUCTION

In late December 2019, a series of atypical pneumonia cases, at the time of unknown origin, were reported in Wuhan, China. Days later, the etiologic agent was identified as a new coronavirus called SARS-CoV-2, and the disease it produced was called COVID-19 (Mojica-Crespo *et al.,* 2020). The viral infection has expanded internationally and the WHO (World Health Organization) announced a Public Health Emergency of International Concern (Esakandari, 2020). The infection caused by this virus rapidly progressed from an isolated outbreak in a Chinese region to a pandemic (Mojica-Crespo *et al.,* 2020). The clinical presentation of COVID-19 may be nonspecific, with symptoms common to other influenza syndromes (Meirelles, 2020). Patients are clinically classified as mild, moderate, severe and critical (Zu, 2020).

Most, about 80% of the cases of COVID-19 are mild, with non-acute symptoms, presenting no evidence of viral pneumonia and hypoxia; 15% of the patients evolve to moderate symptoms, having clinical signs of pneumonia, presenting fever, cough, dyspnea, tachypnea, but no signs of severe pneumonia, with peripheral blood O2 saturation > 90% on room air; 5% of patients present severe forms of the disease, with clinical signs of pneumonia, having fever, cough, dyspnea, tachypnea, and at least one of the following findings: (1) peripheral blood O2 saturation < 90% on room air, (2) respiratory rate > 30 breaths/minute, (3) severe respiratory distress, (4) lesion progression greater than 50% within 24 to 48 hours on chest imaging; and, in a lower incidence, the critical form of the disease, with respiratory failure, cardiovascular shock, and acute renal and/or hepatic failure (Meirelles, 2020; Li, 2020). The COVID-19 pandemic has been associated with a higher prevalence of complications in patients with comorbidities, such as systemic arterial hypertension, coronary disease, diabetes mellitus, obesity, chronic obstructive pulmonary disease (COPD) and asthma (Bastos *et al.,* 2020). In multiple studies, RT-PCR (Real-Time Reverse Transcription Polymerase Chain Reaction), with sample collected from the nasopharyngeal swab, is considered the most widely used test and disseminated by health systems in several countries around the world; however, this test has shown to have low sensitivity, with reported sensitivity of up to 60% in some cases[7]. Although this diagnostic method is widely used for its ability to detect SARS-CoV-2 in respiratory secretions, some studies have reported negative RT-PCR results for COVID-19 at initial presentation, despite typical chest CT findings (Fang *et al.,* 2020). In the clinical context of the disease, such sensitivity is not effective for diagnosis, and some studies have demonstrated the sensitivity of lung CT imaging of approximately 88% (Ai *et al.,* 2020). In diagnosis, chest CT scans may complement the limitations of the RT-PCR (Ye, 2020) examination. Multiple bilateral lobular ground-glass opacities (*GGO-ground glass opacity*) with peripheral distribution, with or without consolidation or visible intralobular signs, reverse halo sign, and other pneumonia findings in organizing are typical features of COVID-19pneumonia CT scans (Bastos *et al.,* 2020; Xu *et al.,* 2020). This examination also allows a more objective and localized evaluation of lung lesions, enabling a better understanding of the pathogenesis and evolution of the disease[5]. The imaging findings on CT vary according to the evolutionary stages of the disease, classifying it into four phases from the onset of symptoms, as illustrated in Figure 1: (A) initial phase, (B) progressive phase, (C) severe phase or peak phase and (D) dissipative phase or absorption phase (Meirelles, 2020; Li *et al.,* 2020).

The initial stage (0–4 days) is characterized by ground-glass opacities, however the CT may be normal. In the progressive stage (5–8 days), ground-glass opacities are diffuse, presenting mosaic paving and consolidation. The peak stage (9–13 days) manifests itself with more prevalent consolidation foci, persistent diffuse ground-glass opacities and mosaic pavement, with some residual parenchymal bands appearing. Finally, the absorption stage (≥ 14 days) depicts the gradual absorption of the consolidation foci, also observing diffuse ground-glass and the absence of mosaic paving [3]. According to the official diagnosis and treatment protocol (6th edition) adopted by the National Health Commission of China, CT scanning is of great importance not only in diagnosing COVID-19, but also in monitoring disease progression and evaluating therapeutic efficacy (Rosa Marcela Emer Egypto, 2020). In a recent retrospective study, quantitative CT analysis performed using the 3D Slicer software made it possible to assess lung damage in a valuable way in determining prognostic implications. Chest CT has proven to be fundamental for the early diagnosis of COVID-19 due to its ability to detect all the characteristics of the disease, and the acquisition of a 3D image generated from it, allowed considerable advances in understanding the pathophysiology of ARDS (*Acute Respiratory Distress Syndrome*) and in establishing adequate oxygenation support, besides being a fast and standardized method, ensuring a thorough evaluation of lung parenchyma involvement (Lanza, 2020). Thus, the need to screen for initial RT-PCR false negatives is crucial, and chest CT scans seems to be an important tool for this purpose. However, there are still no defined image standards for such screening. In this context, the importance of employing the processing of CT images and their respective generation in 3D is again highlighted to improve the diagnosis of this syndrome. Thus, the present study compared tomographic images, through 3D processing using the 3D Slicer (Kikinis, 2014) software platform, of a negative RT-PCR patient with a positive one, in order to collaborate with the diagnosis of COVID-19, including the tomographic evaluation.

MATERIALS AND METHODS

To create the 3D model, the free software 3D Slicer was used, a free extensible software with cross-operating system and open-source code, specialized in 3D reconstruction and visualization, which allows the processing of medical images (Cheng *et al.,* 2016). In a research environment, it is often necessary to create 3D models and even real prototypes (through 3D printing) that allow the exploration and refinement of a new algorithm or concept. The development of the 3D Slicer project started with the goal of providing a common research platform with basic research functionality and has evolved to provide advanced clinical research support (Pieper, 2004). We opted to perform the processing of the 3D images using the 3D Slicer software because it is freely available, and also in order to improve the evaluation of the aspect and the quantity of the images of the evaluated CT scans. In the 3D Slicer, three segments were adopted, referring to the following structures: white segment for the lung; cyan-colored segment for the trachea and bronchus; and blue segment for lesions. The 3D Slicer features a variety of segmentation tools, from fully manual, other semi-automatic, automatic and even refinement tools. In this research, for the delimitation of the lung region, we used the tools “Threshold”, “Islands” and “Smoothing”. The first to be used is the “Threshold”, which is a semi-automatic tool that allows, with the appropriate density adjustment, to select the pulmonary area of interest. This command allows the detection of gray scale limits, as shown in Figure 2. The “Islands” tool was used to exclude previously selected areas that are not of interest during the 3D reconstruction process of the pulmonary region. “Smoothing”, on the other hand, is a smoothing tool, making it possible to eliminate imperfections in the 3D model. Finally, in order to be able to visualize the interior of the lung, an opacity degree of 0.2 was adopted.

For the delimitation of the trachea and bronchus, the tools "Flood Filing", "Smoothing" and "Margin" were used. With the command "Flood Filing" it was possible to segment the trachea and bronchus, isolating them from the global lung segment. The “Margin” tool allowed an improvement in the creation of the 3D model, changing the aspect of the image margins. A logical subtraction operation was applied between the trachea segment (and bronchus) and the lung segment, eliminating the trachea and bronchus from the lung geometry, as shown in Figure 3. For the delimitation of lung lesions, the automatic tool “Grow from Seeds” was first used. However, it was not successful, because in some situations the command failed and in others, after processing, the delimited lesions did not reflect the reality when compared with the tomography image. The solution was to use the “Paint” hand tool, marking the lesions presented in the different sections of the tomography images. Future research may be carried out to find an automatic tool for better delimitation of these injuries, with the objective of obtaining greater precision and efficiency in processing. The “Smoothing” command was also executed to achieve a better smoothing of the lesion regions in the 3D model. Then, an opacity degree of 0.5 was applied, for a better 3D visualization of the lesions. In a universe of more than 170 cases of COVID-19 admitted to the ICU of a private hospital in the city of Curitiba / PR, Brazil between March and August 2020, two patients were blindly selected and paired for sex, age, outcome and hospitalization time, in addition to the presence of RT-PCR and CT scans of the chest on admission. Knowing that the clinical sensitivity is influenced by several factors such as the day of collection in relation to the beginning of the infection, the type of sample used and the clinical manifestations of the patient, we tried to base the sample selection on these criteria. The data from the clinical cases, as well as the images in DICOM format were collected based on the analysis of medical records and data present in the database of the company CEPETI (Center for Studies and Research in Intensive Care), which performs medical coordination of the referred ICU, after previous authorization.

RESULTS

The two cases are presented below, detailing the aspects found.

CASE 1: RT-PCR initially negative, and positive at post-mortem
A 53-year-old male patient with no reported comorbidities. According to nutritional assessment, on admission he had a BMI > 30, obesity being his only detected comorbidity. He was admitted to the ICU with reports of cough, fever, and dyspnea for 7 days (progressive stage)

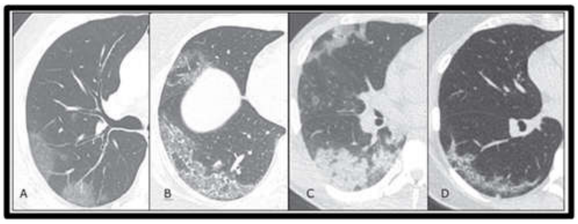

Figure 1: High resolution CT images diagnosed with a COVID-19 diagnosis, illustrating the different stages of the disease. (A) Initial phase, with ground-glass pulmonary opacities. (B) Progressive phase, with pulmonary mosaic paving. (C) Peak phase, with pulmonary consolidations. (D) Absorption phase, with reticular pattern. [SOURCE: MEIRELLES, 2020

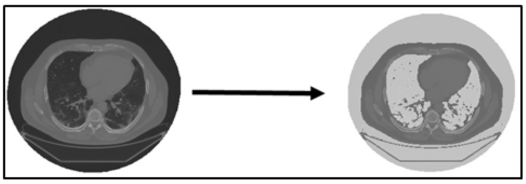

Figure 2. Illustration of the execution of the "Threshold" command (detection of different shades of gray). In this case, the region delimited as white represents the lung

and worsening in the 24 hours before admission. At the time, he had a positive epidemiology for COVID-19 (participation in a business event in which several colleagues tested positive for the disease). RT-PCR was collected from the nasopharyngeal swab onD1 and D5 of hospitalization, both with negative results. Also on D1, a chest computed tomography (CT) scan was performed, with an image highly suspicious of Coronavirus pneumonia according to the radiological report. During hospitalization and evaluation, the patient did not present any other possible or detected diagnoses. Subsequently, the patient presented significant clinical worsening, with no response to the established clinical and supportive treatments, progressing to death on the twelfth day of hospitalization (D12). Due to the absence of diagnostic confirmation by the time of the outcome, a new post-mortem RT-PCR sample was collected, obtaining a positive result for COVID-19.

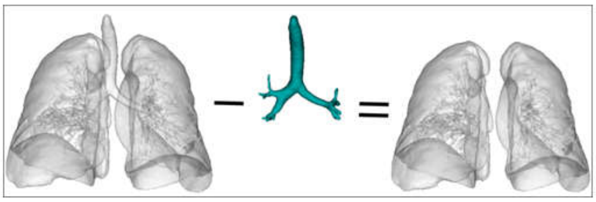

Figure 3. Illustration of the logical operation between the lung segment (in white / gray) and the trachea and bronchus segment (shown in cyan)

CASE 2: Positive RT-PCR since admission to the ICU

A 57-year-old male patient with no reported comorbidities, except for obesity (BMI > 30). He was admitted to the same ICU as case 1, with reports of fever and dyspnea for 5 days (progressive stage), with worsening of the latter symptom in the 48 hours before admission. According to the protocol for suspicious patients, the RT-PCR test was collected from the nasopharyngeal swab on D1, and the result was positive for COVID-19. Chest CT was also performed on the day of hospital admission, with a report compatible with Coronavirus pneumonia. During hospitalization, the patient evolved with significant clinical worsening, with no response to the clinical and supportive treatments instituted, and died on the eleventh day of hospitalization (D11). Through the proposed methodology, three-dimensional models of the entire lung region were obtained, allowing the delimitation of the areas compromised by pneumonia via COVID-19.

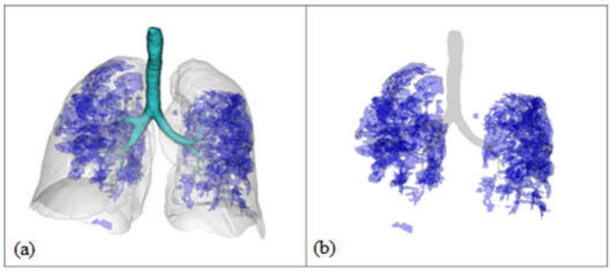

Figure 4. 3D reconstruction of case 1, with negative RT-PCR, illustrating: (a) Complete 3D model and (b) Detailsof the lesion regions selection

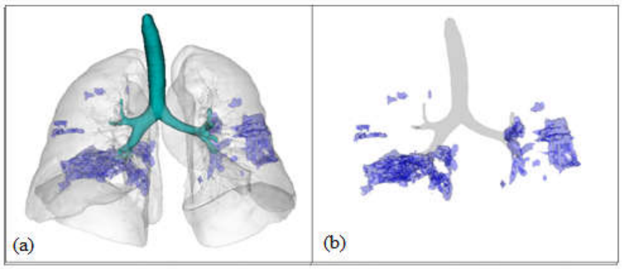

Figure 5. 3D reconstruction of case 2, with positive RT-PCR, showing: (a) Complete 3D model and (b) Detail of the lesion selection

To illustrate the results obtained, Figure 4 shows the complete 3D model, including the delimitation of the regions of lesions for the first case, i.e., RT-PCR negative at first. Figure 5, for the second case, with positive RT-PCR since admission to the ICU.

DISCUSSION

Currently, RT-PCR is the test recommended by the Ministry of Health and by societies around the world for the diagnosis of COVID-19 (Orientações, 2020; Lescure, 2020; Wiersinga, 2019). Despite this, multiple studies show a high rate of false negative (Ai, 2020; Wiersinga, 2019; Kucirka *et al.,* 2020) even when the case shows signs and symptoms typical of the disease. The reason for these false negatives has not yet been elucidated, with hypotheses related to both viral load and the time to onset of symptoms (Ai, 2019; Kucirka *et al.,* 2020). Due to these negative results in patients with a clinical picture compatible with the disease, hospitals have routinely performed a chest CT scan on admission in all patients with a clinical picture requiring hospitalization (severe or critical COVID-19) (Shi, 2020; Chung, 2020; Li, 2020). Such conduct is increasingly frequent due to the high sensitivity of suggestive images for diagnosis (despite low specificity) (Shi, 2020; Chung, 2019; Li, 2020). In general, the sensitivity of chest CT scansare greater than that of RT-PCR. In a study involving 51 patients with chest CT scans and RT-PCR assay, CT sensitivity for COVID-19 infection was 98% compared to RT-PCR sensitivity of 71% ($p < 0.001$). The reasons for the low efficiency of viral nucleic acid detection are associated with the immature development of nucleic acid detection technology, variation in the detection rate of different manufacturers, the low viral load of the patient and / or the inadequate clinical sampling (Xie *et al.,* 2020). In a systematic review with meta-analysis, chest CT scans also showed high sensitivity (91.9%) but low specificity (25.1%), whereas RT-PCR is mentioned as being less sensitive, contributing to the recommendation of different diagnostic tests to achieve adequate sensitivity and specificity (Böger *et al.,* 2021). Based on this information, the hypothesis was raised that, since bothpatients were in the same stage of disease evolution (5 and 7 - progressive stage) and both had severe COVID-19 that progressed to critical, the fact that case 1 had initially negative RT-PCR could be related to the quantity of pulmonary lesions, assuming that they were fewer in quantity/extent, which did not happen.

By observing the generated three-dimensional models, the lung lesions presented on chest CT by the patient in clinical case 1 are more numerous and more diffuse than in case 2 (Figure 4). In comparison, case 2 shows a consolidation in the right lung base, with few lesions in the other lung lobes (Figure 5). Despite such difference, both were considered highly suspect of viral pneumonia by the radiological reports, and in the current context, with high suspicion of SARS-COV2 infection. When comparing the images processed three-dimensionally, we observed that in reality the negative RT-PCR patient initially had a greater number of lesions and more lobes affected than the images presented by the patient with positive RT-PCR since admission, thus refuting our initial hypothesis. The imaging patterns identified in the chest CT scans of both patients resemble the findings described in the literature, namely multiple, bilateral, lobular *ground-glass* opacities (GGO) with a peripheral distribution, these being typical chest CT features resulting from viral pneumonia, properties which, in the context of the pandemic, are highly likely to be associated with the COVID-1910 condition (Shi *et al.,* 2020; Chung, 2020; Li, 2020) which shows good consistency of these data. Chest CT also allows a more objective evaluation of lung lesions, enabling a better understanding of disease progression, since they are classified into four phases: initial, progressive, severe, and dissipative[5], which can be facilitated by a 3D image reconstruction to allow a better identification of these phases. In view of the results obtained, it cannot be said that there is a direct relationship between the affected lung regions and their extension, and the RT-PCR result, which shows the need to triangulate sources of information to support the diagnosis of this not yet fully known syndrome. Despite the non-recommendation by the Brazilian Society of Radiology[25] for routine chest tomography and in the absence of pathognomonic signs on images for the diagnosis of COVID-19, such a test seems to be of paramount importance for the early suspicion and initiation of the most appropriate therapeutic support for patients, even in the presence of negative RT-PCR, according to findings in the literature ((Shi *et al.,* 2020; Chung, 2020; Li, 2020) and reinforced in the present study. Thus, these results corroborate the literature, which shows greater sensitivity of chest tomography for early suspicion of COVID-19 when compared to RT-PCR tests (Ai, 2020; Fang, 2020).

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