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PULMONARY ALVEOLAR LIPOPROTEINOSIS: CASE REPORT

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Abstract: Pulmonary alveolar proteinosis (PAP) is described as a rare disease, characterized by the accumulation of pulmonary surfactant, composed of glycoproteins and lipids, in the alveoli. As a result of this accumulation, the individual may experience everything from dyspnea and hypoxemia to opportunistic infections. The basis of the pathology are disorders of surfactant homeostasis, which can be classified as Primary, Secondary or Congenital etiology. Regardless of the origin, in adults, the main treatment is total lung lavage (TPL). In addition to being the most widespread, lowest-cost and most accessible treatment option, it is capable of bringing immediate relief to the patient's symptoms.**Objective**: To report the case of a patient undergoing lung lavage at Messejana Hospital, for the treatment of dyspnea. **Methods**: Retrospective and descriptive report, using data from medical records, imaging exams and photographic records of the procedure, in addition to a literature review in PubMed databases, covering publications from 2019 to 2024. **Results**: A 25-year-old man was diagnosed with PAP after chest x-ray revealing bilateral infiltrates. After two years, he developed progressive symptoms, including dyspnea and persistent cough, leading to whole lung lavage (LPT) being performed twice, resulting in immediate improvement in symptoms. **Final considerations**: LPT is effective in symptomatic relief of PAP. A multidisciplinary approach and close monitoring are necessary for better recovery.

Keywords: Pulmonary alveolar proteinosis; Pulmonary alveolar lipoproteinosis; Lung lavage.

INTRODUCTION

The Pulmonary alveolar proteinosis (PAP) is a rare syndrome composed of a heterogeneous group characterized by disturbances in the production or clearance of surfactant, which accumulates inside the alveoli and impairs the gas exchange process to different degrees. It was first described in the 1950s and recent advances have significantly improved the understanding of pathogenesis, clinical subtypes, treatment and prognosis 1.

The distribution is worldwide with a prevalence of between 6.87 cases per million, and the incidence is estimated at almost 0.2 cases per million. It occurs most commonly in adults, with an average age between 40 – 50 years, but can be found in neonates, infants and children. There is a predominance of males with a prevalence ratio of approximately 2:1, and a relationship with smoking is also observed 2.

Currently, PAP can be divided into three classes: Primary, Secondary and Congenital. Primary PAP is caused by interruption of granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling, whose function is to regulate surfactant clearance by alveolar macrophages. In this case, one can find the Autoimmune clinical subtype (corresponding to > 90% of all PAP cases and marked by the serum presence of the anti-GM-CSF autoantibody) and the Hereditary clinical subtype (less than 3% of cases, characterized by mutations in the genes encoding GM-CSF receptors). Secondary PAP (around 5–10% of cases) occurs due to relative deficiency of GM-CSF and dysfunction of alveolar macrophages caused by various factors such as chronic infections, inhalation of toxic substances, immunological defects and hematological dyscrasias (myelodysplastic syndrome and deficiency of GATA2, for example). Congenital PAP (1-2% of cases) is caused by surfactant production disorders,

involves several genetic variants and generally manifests itself in newborns 3.

The symptoms of PAP are quite nonspecific and can range from asymptomatic disease to death in the first days of life in newborns, depending on the nature of the genetic defect. The most common symptoms are progressive dyspnea, productive or dry cough and fatigue 4.

I describe below the case of a completely asymptomatic patient who was identified only through a mandatory health screening protocol, but with symptoms appearing two years after diagnosis. Due to significant worsening over time, intervention with lung lavage (LP) was necessary.

METHODS

Retrospective, descriptive case report, involving a single patient, with case discussion and literature review. Data collection was carried out based on documentary analysis of the medical records, as well as complementary image exams and photographic records of the procedure to which the patient underwent. The bibliographic survey was carried out using the Pubmed database, using the following descriptors in Health Sciences (DeCS)/ MeSH- Medical Subject Headings: "pulmonary alveolar proteinosis", "pulmonary alveolar lipoproteinosis" and "pulmonary lavage".

Only complete international articles in the English language, published in the last five years (2019-2024), freely available, that addressed aspects related to the epidemiology, etiology, diagnosis, treatment and outcomes of pulmonary alveolar proteinosis were included.

Articles with clinical studies on animals, focus on the pediatric population, samples of patients with associated lower prevalence comorbidities and predominance of treatment options that did not involve lung lavage were excluded.

From a total of 45 articles examined, after inclusion and exclusion criteria, 12 articles were selected to serve as a theoretical basis and discussion.

RESULTS

CLINICAL HISTORY

A male patient, aged 25 years, underwent chest radiography (X-ray) for admission examination, which showed the presence of bilateral infiltrates. He decided to continue with the investigation only at the age of 27, still asymptomatic. At a reference service in Rio de Janeiro, he underwent chest computed tomography (CT) and bronchoscopy. The radiological image showed a mosaic paving pattern. During a diagnostic bronchoscopy, milky liquid came out, with the result of the lavage study being negative for the search for neoplastic cells, negative for the direct search/culture of microorganisms and fungi. Microscopy, however, demonstrated amorphous granular material and alveolar macrophages with positive periodic acid-Schiff (PAS) staining, establishing the diagnosis of PAP.

Initially, follow-up was only conservative, given the absence of symptoms. However, over the years, the patient began to experience asthenia, progressive dyspnea, dry cough and weight loss (a total of 28kg between 2016 and 2021). At the age of 30, he was hospitalized due to dyspnea at rest and persistent cough with hyaline sputum, and underwent total lung lavage (TPL). At the age of 32, once again with a progressive and disabling worsening of symptoms, he needed to be hospitalized again to repeat the procedure. On both occasions, there was complete improvement in the condition the following day.

Within his personal history, he worked as a farmer from his adolescence until the age of 25, when he began working as a bricklayer's assistant. He ended this activity at the time

of the diagnosis of alveolar proteinosis. There was no history of pulmonary tuberculosis, smoking or exposure to smoke. The family history was poor and there were no pertinent exhibits. On physical examination, he was emaciated, had mild tachydyspnea at rest, and had an oxygen saturation of 95% on room air. On lung auscultation, he had discrete crackles in the lower 2/3 of both lungs. The ELISA test for HIV was non-reactive.

RADIOLOGICAL FINDINGS

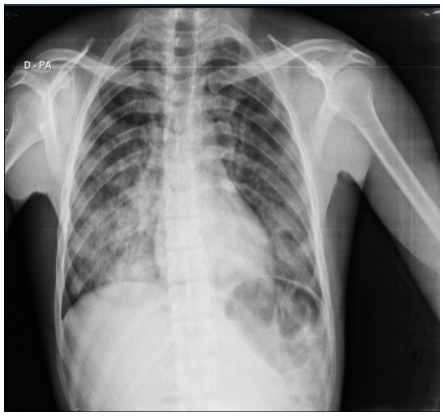

Figure 1: Chest X-ray on admission: bilateral heterogeneous and irregular infiltrates, more significant on the right. (source: own author)

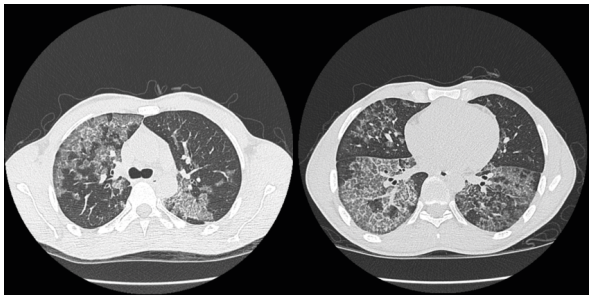

Figure 2: High-resolution computed tomography (HRCT) of the chest during hospitalization, before the procedure: ground-glass opacities with diffuse distribution, with thickened interlobular septa (mosaic paving pattern). (source: own author)

PROCEDURE

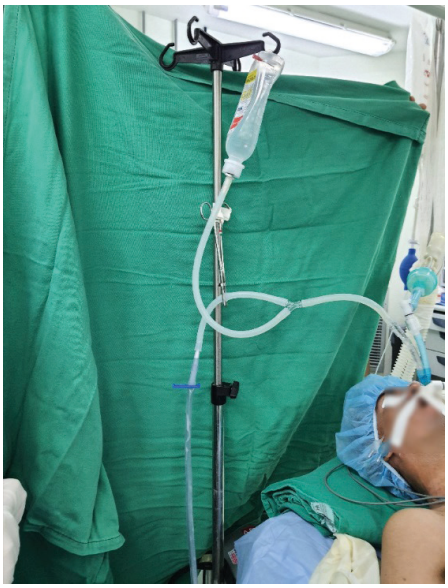

Figure 3: Partial lung lavage on the right, in a surgical center, under general anesthesia, with a double-light orotracheal tube and left unilateral ventilation. (source: own author)

Figure 4: Bottles with the alveolar lavage resulting from the procedure. It was observed that the aspirated liquid was progressively less cloudy and less foamy (from left to right). In total, 12L of 0.9% saline solution were used. (source: own author)

DISCUSSION

Surfactant is a liquid produced by type II alveolar epithelial cells (AEC-II) whose composition is 90% phospholipids with 10% proteins. It performs the function of reducing the surface tension of the alveoli, which prevents their collapse. The whitening of this substance is carried out in part by the AEC-II itself, but predominantly by the uptake and catabolism carried out by alveolar macrophages. To develop this function, macrophages are regulated through GM-CSF signaling, a cytokine also produced by AEC-II 5. Another extremely important role of GM-CSF is related to lung and blood immunological function. In addition to stimulating myeloid maturation for the differentiation of precursor macrophages into alveolar macrophages, this cytokine also acts in a pro-inflammatory manner on blood neutrophils, increasing phagocytosis and cellular recruitment. Defects in this pathway increase pulmonary/systemic susceptibility to a wide variety of microbial pathogens such as bacteria, viruses, fungi and parasites [4, 5, 6].

Therefore, both the presence of GM-CSF and the correct functioning of its receptor on the macrophage membrane are fundamental for surfactant homeostasis. The various clinical subtypes of PAP develop from impairment in one of these processes [7].

The pathogenic mechanism of **primary PAP** is the disruption of GM-CSF signaling, whether due to autoimmunity (autoimmune) or a defect in the receptor (hereditary). **Autoimmune PAP** is the most common clinical form in adults, representing around 90-95% of cases. Its prevalence is 7-10 individuals per million, with no preference for ethnicity, being twice as common in men and typically occurring between the third and sixth decade of life 1, 2. The ratio is 50-70% with smoking may reflect the historically greater exposure of this habit in the male population and not necessarily a propensity due to sex. Anti-GM-CSF are composed of IgG, highly specific for GM-CSF and capable of inactivating high concentrations of cytokine [4].

Hereditary PAP comprises less than 3% of cases and is related to the interruption of GM-CSF signaling by recessive mutations in the α and β genes of the GM-CSF receptor (CSF2RA or CSF2RB) 4. It shares clinical and radiological findings with autoimmune PAP and histologically similar, requiring genetic mapping to differentiate them. The samples for studying this group are very small, given the rarity of a disease that is already uncommon[3,5].

Secondary PAP comprises 5–10% of adult PAP with a prevalence of approximately 0.5 per million. It is associated with some disease, environmental exposure or toxic substance that negatively impacts the number and function of alveolar macrophages. The main condition found is hematological disorders (myelodysplastic syndrome, leukemia, lymphoma, aplastic anemia, among others), identified in 75% of cases. Associations with immunological diseases (acquired immunodeficiency syndrome, severe combined immunodeficiency, monoclonal gammopathy, among others), non-hematological malignancies (lung adenocarcinoma, glioblastoma, melanoma), infections (Cytomegalovirus, Mycobacterium tuberculosis, Nocardia, Pneumocystis jiroveci, among others) are also described), inhalation of inorganic dust (silica, cement, titanium and aluminum, among others), inhalation of organic dust (sawdust, fertilizers, bakery flour and others) and inhalation of vapors (chlorine, varnish, paint and others). The pathogenic mechanisms that cause secondary PAP have not yet been clarified, but the prognosis is worse than that of autoimmune PAP [4].

Congenital PAP (2% of cases) is characterized by a genetic mutation in the production of surfactant proteins, generating a dysfunctional end product that is difficult

to catabolize and accumulates in the alveolar space. As this is a more specific topic in pediatrics, it will not be part of the scope of this work [3].

The age at which clinical manifestations appear and the severity of the disease usually vary according to the underlying clinical subtype. In general, the symptoms are quite nonspecific and insidious, with progressive dyspnea, cough and fatigue being more common. Occasionally, there is the presence of white frothy or gelatinous sputum. Fever may be present either due to an associated underlying clinical condition or due to intrinsic susceptibility to infections. Up to a third of patients may be completely asymptomatic at the time of diagnosis. The physical examination is usually poor, but crepitus and digital clubbing may be found (50% and 25% of cases, respectively) [2].

Pulmonary function tests (PFT) show a restrictive pattern in more advanced conditions. Reduced diffusing capacity for carbon monoxide (DLCO) is a more useful and earlier indicator of severity [4].

Chest X-ray usually demonstrates diffuse bilateral infiltrates, with the bat wing sign frequently occurring, with symmetrical perihilar opacity. Chest CT is marked by diffuse ground-glass opacities (VF) accompanied or not by interlobular septal thickening – a pattern known as mosaic paving 3. At this point, it is necessary to evaluate and rule out diagnostic possibilities that may present a similar tomographic pattern, such as pneumonitis hypersensitivity, Pneumocystis jiroveci pneumonia, minimally invasive/lepidic invasive adenocarcinoma, lymphangitic carcinomatosis, cardiogenic pulmonary edema and acute respiratory distress syndrome [5].

The most common laboratory alteration is elevated levels of lactate dehydrogenase (LDH), however this finding is quite nonspecific. Several biomarkers for correlation with disease severity are in the research phase (SP-A, SP-D, KL-6, CEA, Cyfra 21-1 and YKL-40)[2].

The rarity of the disease associated with non-specific symptoms strongly contributes to delays in diagnosis, which can take years. Suspicion must be raised in cases with compatible clinical history and radiological findings [5].

Bronchoscopy is a highly helpful exam for investigating PAP and is becoming increasingly indispensable. Most of the time, the diagnosis is made based on the findings of this procedure associated with the clinical presentation and the HRCT pattern. BAL is characteristically milky. Its microscopic study reveals the presence of foamy macrophages and a dirty-looking segment, which is positive for periodic acid-Schiff (PAS) staining.

Transbronchial biopsy increases diagnostic yield and reduces the need for surgical biopsy, which is practically no longer necessary. At the same time, BAL makes it possible to investigate other etiologies, being able to find or rule out associated conditions, such as infectious ones, for example [4, 8].

To define the etiology of PAP, the first test to be performed must be serum anti-GM-CSF dosage, since autoimmune PAP is the most common etiological cause. A value >19mcg/mL confirms the condition and a value <10mcg/mL has a negative predictive function. It is a well-validated test, with 100% sensitivity and specificity for autoimmune PAP. On the other hand, it is an expensive test and restricted to large research centers [2, 4, 7].

Detailed medical history and investigation into occupational and environmental exposure are critical to identifying any possible causes of secondary PAP in the case of normal GM-CSF autoantibody levels. Once an underlying condition has been ruled out, the next step is to measure the serum level of GM-CSF and test whether its signaling is working [3].

Deficient signaling combined with high levels of GM-CSF points to hereditary PAP, and research for CSF2RA or CSF2RB mutations is recommended. If both tests are normal, the hypothesis is congenital PAP, making it necessary to analyze genetic mutations in the production of surfactant proteins [8].

On some occasions, despite all possible investigation, the etiology of PAP cannot be attributed to a known cause. In this case, PAP is called unclassified [3].

The severity of the disease and etiological identification will guide the choice between treatment options. Asymptomatic patients or those with mild symptoms can only be monitored periodically and do not require any specific therapy. On the other hand, cases in which there is dyspnea on slight exertion and/or hypoxemia deserve treatment [9].

For autoimmune PAP, there are at least three possible therapies: increasing GM-CSF levels beyond the ability to neutralize the antibodies (using subcutaneous or nebulized GM-CSF), removing antibodies from the blood circulation through plasmapheresis, or blocking the production of autoantibodies through the destruction of B lymphocytes (use of rituximab). Among these, the most robust evidence is the use of recombinant GM-CSF, with success rates of approximately 50% for subcutaneous administration and 60% for inhalation[7]. The other options are used as rescue therapy in refractory cases.

The basis of treatment in cases of secondary PAP is to address the underlying cause, and lung lavage may be useful in some situations.

Regardless of origin, in adults, the gold standard treatment is total lung lavage (TPL). In addition to being the most widespread, lowest-cost and most accessible therapeutic resource, it is capable of bringing immediate relief to the patient's symptoms. The indication criteria are mainly disease progression and dyspnea that limits daily activities [10].

LPT consists of the mechanical removal of excess surfactant using the instillation and subsequent gravity drainage of high volumes of saline solution heated to 37°C. Up to 50 liters can be used in each lung, instilled in volumes of 500 to 1000ml per cycle. Each infusion and drainage series take 3 to 5 minutes. The defining criterion for ending LPT is the visual improvement of the lavage effluent 1. The patient must be intubated with a double-lumen tracheal tube, under general anesthesia, in single-lung ventilation, with the presence of an experienced respiratory endoscopist. In some cases, extracorporeal membrane oxygenation (ECMO) support may be necessary [11].

In general, the procedure is performed first on the most affected lung, followed by lavage of the second lung 1-2 weeks later. Although invasive, it is a safe procedure, with a complication rate of around 18%, the main ones being: fever, hypoxemia, pneumothorax, hydrothorax, minor bleeding due to airway injury and acute respiratory distress syndrome[8].

Despite its wide use, LPT is not standardized, with a lack of clarity regarding technical aspects (such aspatient position, lung selection, total lavage volume, chest percussion) and even in relation to indications and contraindications. The effectiveness of the procedure varies greatly according to the experience and techniques used in the operating center [12].

Although there is improvement in lung function and symptoms in most patients, there may be a recurrence rate of 30-70%, and it may be necessary to repeat sessions due to the reaccumulation of surfactant [6].

The patient in the current case received lung lavage with 12 liters of heated 0.9% saline solution, along with chest percussion maneuvers to redistribute the liquid. During postoperative recovery, he was extubated in the operating room, observed in the ICU for

one day, and was discharged within 24 hours without dyspnea. The left lung was scheduled for lavage at a later stage, electively.

Lung transplantation is an option to be considered for selected patients with progressive disease unresponsive to the described therapies, with the main concern being recurrence in allograft [4].

FINAL CONSIDERATIONS

This case reinforces the effectiveness of whole lung lavage (LPT) in providing significant and rapid symptomatic relief for patients with Pulmonary Alveolar Proteinosis (PAP), even in cases of progressive and debilitating symptoms. Experience highlights the importance of a multidisciplinary approach, rigorous monitoring and use of appropriate techniques to minimize complications during the procedure, ensuring an efficient and safe recovery for the patient.

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CONSUBSTANTIATED OPINION OF THE C.E.P.

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CONSUBSTANTIATED OPINION OF THE CEP

CT DATA
Research title: pulmonary Alveolar Lipoproteinosis: case report
Researcher: SIMONY SAMPAIO SOARES de OLIVEIRA
Thematic Area:
Version: 2
CAAE: 80901224.8.0000.5039
Proposing institution: Hospital de Messejana Dr. Carlos Alberto Studart Gomes
Main Sponsor: Own Funding

OPINION DATA
Opinion number: 6,993,266
Project presentation:
PB_BASIC_INFORMATION OF_PROJECT_2347194.pdfintroduction: Pulmonary alveolar proteinosis (PAP), is described as a rare disease characterized by the accumulation of pulmonary surfactant, compound by glycoproteins and lipids, in the alveoli. As a result from this accumulation, the individual may present from dyspnea and hypoxemia to opportunistic infections. The pilarda pathology is the disorders of surfactant homeostasis, and can be classified as of etiology Primary, secondary or congenital. Regardless of the origin, in adults, the main treatment is total lung lavage (TPL). In addition to being the most widespread treatment option, lower cost and more affordable, it is able to bring immediate relief of the patient's symptoms. Purpose: to report the case of a patient submitted to partial lung lavage in the hospital of Messejana, for treatment of dyspnea. Methodology: Active search of clinical-epidemiological and socio-environmental data present in the archives of the Messejana, in the medical record of the patient in question. Purpose of research: Primary Objective: To report the case of a patient submitted to partial lung lavage in the hospital of Messejana, to treatment of dyspnea.

Purpose of research:
Primary Objective:
To report the case of a patient submitted to partial lung lavage in the hospital of Messejana, to treatment of dyspnea.
Secondary Objective

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Continuation of opinion: 6,993,266
Describe the clinical and Radiological presentation of pulmonary alveolar
Describe the lung lavage procedure
Assessment of risks and benefits:
There will be no physical or psychological risks to the patient as there will be no contact with it.
The risks are inherent in the loss of medical records.
Benefits:
Regarding the benefits, they will be numerous in view of the fact that it is a rare case with a wide range differential diagnosis, and this study may contribute to better care of patients in similar conditions and, consequently, better therapeutic protocols a posteriore.
Comments and Considerations on the survey: The present study consists of in a case report, which is considered, according to Gil (2010), as a study of one or a few objects, in a way that allows its broad and detailed related knowledge to a theme. It is a common type of study, didactic and widely used in events scientific conferences, symposia and publications in journals. Case Reports allow description detailed analysis of clinical cases, which are extremely important, containing features such as signs, symptoms, information on therapeutic procedures and above all, the course of the case. They are indicated in rare situations and or that are not clearly established in the scientific literature. This type of study was chosen to suit the needs of the proposal intended by the author. The research will be carried out in the period of May and June 2024 at the hospital De Messejana Dr. Carlos Alberto Studart Gomes, located in the city of Fortaleza, state of Ceará. The study unit will be the pulmonology ward, in which the beginning of the collection of data in the period from May 2024.

Considerations on the terms of mandatory submission:
All present terms
Recommendations:
No recommendations

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Continuation of opinion: 6,993,266

Conclusions or pending and list of inadequacies:
No pending
Final considerations at the discretion of the C.E.P.:
The researcher must go to the Clinical Research Unit, equipped with of this document, to receive the badge and start data collection. After the completion of the research, the researcher must send a to this Committee a report with the results and conclusion.

This opinion was prepared based on the documents listed below:

Document Type	Archive	Post	Author	Situation
Basic information the Project	PB_INFORMAÇÕES_BASICAS_DO_PROJETO_2347194.pdf	17/07/2024 14:00:57		Accepted
Other	CRONOGRAMA_ATUALIZADO.pdf	17/07/2024 14:00:34	SIMONY SAMPAIO SOARES DE OLIVEIRA	Accepted
Other	CONFIDENCIALIDADE.pdf	17/07/2024 14:00:01	SIMONY SAMPAIO SOARES DE OLIVEIRA	Accepted
Other	COMPROMISSO.pdf	17/07/2024 13:59:18	SIMONY SAMPAIO SOARES DE OLIVEIRA	Accepted
Detailed Design / Brochure Researcher	PROJETO.pdf	10/06/2024 11:01:32	SIMONY SAMPAIO SOARES DE OLIVEIRA	Accepted
Other	DEPOSITARIO.pdf	10/06/2024 10:56:38	SIMONY SAMPAIO SOARES DE OLIVEIRA	Accepted
Other	ACEITE.pdf	10/06/2024 10:55:24	SIMONY SAMPAIO SOARES DE OLIVEIRA	Accepted
Other	ANUENCIA.pdf	10/06/2024 10:54:44	SIMONY SAMPAIO SOARES DE OLIVEIRA	Accepted
TCLE/Terms of use Assent / Justification of Absence	TCLE.pdf	10/06/2024 10:50:07	SIMONY SAMPAIO SOARES DE OLIVEIRA	Accepted
Budget	ORCAMENTO.pdf	10/06/2024 10:49:08	SIMONY SAMPAIO SOARES DE OLIVEIRA	Accepted
Timeline	CRONOGRAMA.pdf	10/06/2024 10:43:55	SIMONY SAMPAIO SOARES DE OLIVEIRA	Accepted

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Continuation of opinion: 6,993,266

Title page	Folha_de_Rosto.pdf	10/06/2024 10:42:30	SIMONY SAMPAIO SOARES DE OLIVEIRA	Accepted

nion:
Approved

Does it need an assessment from CONEP?
No

Fortaleza, August, 8, 2024

Signed by:
Armenia Uchôa Mosque
(Coordinator)

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