1. Introduction

Clinical characteristics and radiological pattern of SARS-CoV-2 infection have been widely described in the literature [1]. However, findings are not pathognomonic and are observed in other diseases such as viral pneumonia (influenza A and B, adenovirus, and cytomegalovirus), interstitial pneumonia (organizing pneumonia, chronic eosinophilic pneumonia, and hypersensitivity pneumonia), Pneumocystis jirovecii pneumonia, diffuse alveolar hemorrhage, pulmonary edema, and pulmonary alveolar proteinosis (PAP) [2], an infrequent, underdiagnosed disease. The most common type of PAP is idiopathic; although PAP can also occur as a secondary phenomenon, resulting from inhalation of substances and infectious agents, and it has been associated with hematological malignancies [3].

We present the case of a patient admitted for pneumonia due to SARS-CoV-2 infection who developed PAP, and we describe the approach undertook to determine whether PAP was a consequence of COVID-19 or a fortuitous event.

2. Case Presentation

The patient is a 51-year-old woman from Peru who had been living in Spain for the previous 2 years. Her medical history was unremarkable, and she had no toxic habits. She worked as a seamstress and denied exposure to organic or inorganic toxic pulmonary agents.

In the last year, she reported dyspnea on moderate effort and coughed white mucus, although she did not consult a physician.

She went to the emergency room with severe dyspnea and asthenia. The patient’s vital signs were tachycardia, tachypnea, peripheral oxygen saturation was 65% on room air, and afebrile. The polymerase chain reaction (PCR) test was positive for SARS-CoV-2. A chest X-ray revealed predominantly right-sided bilateral alveolar interstitial infiltrates (Figure 1). Laboratory investigations showed lymphopenia (1100 cells/μL), high D-dimer (590 μg/L), lactic dehydrogenase of 849 units/L, and C-reactive protein of 73 mg/L. The patient was transferred to the intensive care
volumes: forced expiratory volume in 1 second (FEV1),
demayed a mild restrictive ventilatory defect with small lung
easiness such as immunodeficiency (HIV), autoimmune dis-
A systemic study enabled us to rule out underlying dis-
such as immunodeficiency, inhalation of toxic
Abnormalities in macrophages and alveolar neutrophils
increase the risk of opportunistic infections, which may
A whole lung lavage (WLL) was programmed. Given the
severity of lung involvement, a sequential lavage of both
lungs was performed in the same session in combination
with extracorporeal membrane oxygenation (ECMO). No
complications were reported [4] (Figure 3).
One month after the WLL took place, the spirometry
revealed an improvement of 14% in DLCO and a significant
improvement in the crazy-paving pattern on the CT scan,
although all the lung lobes continued to be involved
(Figure 4). A serology with anti-granulocyte-macrophage
colony stimulating factor (anti-GM-CSF) antibodies was
requested, yielding a doubtful cut-off of 2.4 U/mL (positive,
As pulmonary lesions continue to display on the CT
scan, a cryobiopsy was performed to rule out other diseases
associated with well-structured lung parenchyma. The histo-
pathology revealed no abnormalities that would confirm the
diagnosis.
Five months after the initial diagnosis, a new CT scan
revealed a considerable improvement in lung parenchyma
(Figure 4) and normalization of pulmonary function, as fol-
lows: FEV1, 2040 L (98%); FVC, 2370 L (88%); FEV1/FVC,
86; and DLCO, 80%.

3. Discussion

PAP is a rare lung disease characterized by abnormal accu-
mulation of PAS-positive lipoprotein in alveolar spaces and
terminal bronchioles. The estimated incidence is 0.24-0.49
cases per million inhabitants, and the prevalence is 2.04-6.2
cases per million inhabitants [5]. Males are more commonly
affected than females at a 2:1 ratio. The median age of diag-
nosis is 50 years [6]. It usually presents as progressive dys-
pnea and cough that may be accompanied by fever, pain,
and/or hemoptysis, although a third of patients may be
asymptomatic. PAP may be idiopathic, secondary, and con-
genital. Idiopathic PAP is the most common; it accounts for
90% of cases and generally has an autoimmune basis. Anti-
GM-CSF antibodies cause macrophage dysfunction that
result in impaired clearance of surfactant, leading to accu-
mulation. This group also includes hereditary PAP (<1%)
due to mutations in the GM-CSF receptor genes (CSF2RA
and CSF2RB). Secondary PAP (5-10%) is associated with
hematological cancers (lymphoma, leukemia, and myelodys-
plastic syndrome), immunodeficiency, inhalation of toxic
substances, and infection. Congenital PAP is caused by
mutations in genes involved in surfactant production and is
the least common [3].

Abnormalities in macrophages and alveolar neutrophils
increase the risk of opportunistic infections, which may
affect onset of PAP and alter its course. Opportunistic infec-
tion is reported in 5% and 20% of cases, the most common
agents being Nocardia, Mycobacterium tuberculosis, Myco-
bacterium avium-intracellulare, Pneumocystis jirovecii,
Epstein-Barr virus, and cytomegalovirus [7, 8]. PAP has also
been associated with influenza virus, although few cases have
been reported [9]. There are very few reported cases of asso-
ciation between PAP and SARS-CoV-2 to date [10, 11].
Surbhi et al. described a patient with a diagnosis of autoim-
mune PAP who had received treatment with WLL and GM-
CSF. The patient presented an infection with COVID-19,
requiring admission to the ICU with an uncertain prognosis.
Although a clinical worsening of the patient was described,
there was no impact in the evolution of PAP.

In the case we have described, we cannot assign the
patient to any specific group. Anti-GM-CSF antibody levels
were unclear, probably because the test was performed 1
month after WLL. A decrease in levels after the technique
has been reported [12].

Despite the uncertain result, we highly suspect primary
PAP is exacerbated by SARS-CoV-2 infection, since the
patient had mild symptoms (dyspnea and cough) prior to

Figure 1: Chest X-ray on admission. Note the bilateral interstitial
pattern with bilateral diffuse lung involvement.
the infection. In addition, we have not found other causes to justify hereditary PAP (negative genetic study) or secondary PAP (no exposure to inhaled substances or known hematological diseases).

The most common pattern in CT scans in alveolar proteinosis is ground-glass areas superimposed on the thickening of the interlobular and intralobular septal lines, resulting in a crazy-paving pattern [13]. The most frequent radiological
patterns for COVID-19 have been bilateral ground-glass opacities with or without consolidation and/or a crazy-paving pattern [2]. This can generate confusion and diagnostic delay, as in the case we have reported.

The diagnosis of PAP is usually based on a compatible medical history accompanied by typical CT images with milky bronchoalveolar lavage fluid and a positive PAS reaction [13]. Lung biopsy should be considered in patients whose radiological or bronchoalveolar lavage findings are not characteristic. This approach shows the alveoli to be occupied by acellular, amorphous, eosinophilic material (seen clearly with PAS staining), and foamy alveolar macrophages [6].

Mild and moderate forms of PAP require monitoring, since spontaneous resolution has been described. Severe PAP, on the other hand, is generally treated with WLL, which was first reported more than 40 years ago. This technique consists of selective intubation with a double lumen tube, instillation, and reabsorption of saline solution to remove accumulated surfactant [13]. In recent years, variations have been described with simultaneous use of ECMO in severe cases, enabling the sequential lavage of both lungs in the same session [4]. In the case above, the patient opted for this technique due to her poor DLCO (28%).

The therapeutic benefit of inhaled or subcutaneous GM-CSF analogs remains understudy. A favorable response has been reported in 50-60% of patients in clinical trials [4]. Data from a clinical trial show that rituximab did not improve reduced anti-GM-CSF antibody levels [14]. Lung transplantation is reserved for patients who have not responded to previous treatments. Experience is scarce, and recurrences have been observed in lung recipients [15].

PAP has a variable clinical course ranging from spontaneous resolution to death by pneumonia or respiratory failure [16]. The survival rate exceeds 80% at 5 years [17]. The patient we have described is currently being followed up as an outpatient. She remains asymptomatic and does not require oxygen therapy. Her spirometry results are normal, and CT shows almost complete resolution.

In conclusion, it is important to make a correct differential diagnosis of PAP with other conditions that may present clinical and/or radiological pictures similar to those of SARS-CoV-2 infection.

Data Availability

The data used to support the findings of this study are included within the article.

Consent

The patient gave her written informed consent for publication of the case.

Conflicts of Interest

The authors report no conflicts of interest.

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