INTRODUCTION

Common variable immunodeficiency (CVID) is a rare immune system disorder characterized by primary antibody deficiency that leads to hypogammaglobulinemia. It affects between 1:25,000 and 1:196,000 patients worldwide and is usually diagnosed during the age range 20–45 years, although it can be identified earlier [1]. The cause is unknown, but a genetic mutation has been identified in around 10% of cases [2]. The diagnosis is based on biologic examinations and the differential diagnosis with other causes of hypogammaglobulinemia. In case of CVID, serum levels of immunoglobulin (Ig) G are below the age-adjusted reference range on two samples more than 3 weeks apart (or on a single measurement if their level is very low) [3]. The levels of immunoglobulins A and/or M also are decreased. Infectious complications are the main manifestations, mostly affecting respiratory tract and lungs and frequently resulting in the development of bronchiectasis. In addition, CVID patients can develop autoimmune,
A 47-year-old female patient, known for thalassemia trait and glucose-6-phosphate dehydrogenase deficiency was admitted to the Internal Medicine ward for respiratory failure in August 2021.

In 1996, the diagnosis of common variable hypogammaglobulinemia associated with functional deficit of T lymphocytes was made and since then she has been in replacement treatment with monthly infusion of immunoglobulins. She reported repeated infectious episodes of the upper and lower respiratory tract in her remote medical history. She also reported previous laparotomy for appendectomy and hemoperitoneum from hemorrhagic corpus luteum and multiple hospitalizations for muscle and paravertebral abscess localizations subjected to surgical toilet and external drainage. In 2006, she underwent splenectomy and partial pancreatectomy for multiple abscess collections. For some years, she was known for multifactorial pulmonary hypertension and at admission she was in therapy with macitentan and sildenafil. In March 2020, she was hospitalized for SARS-CoV-2 pneumonia.

In her last visit in the Rare Disease Center, in April 2021, clinical stability was reported and her pulmonary hypertension was categorized as World Health Organization (WHO) class I. Furthermore, home O₂ was prescribed, but self-suspended thereafter due to reasons associated with subjective well-being. The problem was no longer evaluated.

On the 17th of August 2021, she was sent to the Emergency Department by her general practitioner due to worsening dyspnea and low-grade fever for about 10 days and associated with productive cough. Blood tests showed high levels of white blood cells (WBCs) and C-reactive protein (CRP) (Table I).

Chest X-ray (Figure 1) and chest CT (Figure 2), compared with the previous tests available, showed an unchanged picture of bilateral bronchiolitis characterized by millimetric centerlobular nodulations partly confluent and by thickening areas located in the medial segment of the middle lobe, in the lingula and in the postero-basal regions of both lower lobes, with greater extension...

### Table I. Patient’s clinical parameters at admission, in August 2021.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Detected level</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (n/L)</td>
<td>22.050</td>
<td>4000–10,000</td>
</tr>
<tr>
<td>RBC (×10⁹/μL)</td>
<td>5.77*</td>
<td>3.6–5.3</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>6</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>12.3</td>
<td>11.0–15.0</td>
</tr>
<tr>
<td>Globular volume</td>
<td>74.1**</td>
<td>80–96</td>
</tr>
<tr>
<td>Neutrophil granulocytes (%)</td>
<td>56.1</td>
<td>40–74</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>38.2</td>
<td>19–48</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>4.4</td>
<td>3.4–9.0</td>
</tr>
<tr>
<td>Eosinophil granulocytes (%)</td>
<td>0.8</td>
<td>0–7</td>
</tr>
<tr>
<td>Basophilic granulocytes (%)</td>
<td>0.4</td>
<td>0–1.5</td>
</tr>
<tr>
<td>Platelets (×10⁹/μL)</td>
<td>817**</td>
<td>150–400</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.74</td>
<td>0.51–0.95</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>18</td>
<td>8–41</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.25</td>
<td>&lt;1.2</td>
</tr>
<tr>
<td>Lactate dehydrogenase (IU/L)</td>
<td>163</td>
<td>125–220</td>
</tr>
<tr>
<td>Total protein (g/dL)*</td>
<td>5.6</td>
<td>6.0–8.0</td>
</tr>
<tr>
<td>IgM (mg/dL)**</td>
<td>&lt;5</td>
<td>40–230</td>
</tr>
<tr>
<td>IgA (mg/dL)**</td>
<td>&lt;5</td>
<td>70–400</td>
</tr>
<tr>
<td>IgG (mg/dL)*</td>
<td>215</td>
<td>700–1600</td>
</tr>
</tbody>
</table>

In recent years, several cases of CVID have been reported to be associated with elevations in pulmonary artery pressures [4-7]. Treatment is based on intravenous or subcutaneous Ig replacement therapy.

Patients with rare diseases are necessarily managed by dedicated centers, but sometimes they are referred to Internal Medicine wards, thus allowing an adequate monitoring of rare disease-related pathologies and complications arising from rare disease-related predispositions.

### Figure 1. Chest X-ray performed in August 2021.

SX = left
DISCUSSION

CVID, a primary antibody deficiency characterized by hypogammaglobulinemia, is known to cause infectious, inflammatory, and autoimmune manifestations. CVID is not a single disease but rather a collection of hypogammaglobulinemia syndromes resulting from many genetic defects. In about 25% of cases, specific molecular defects have been identified, although in most patients, the causes are unknown [8]. CVID has been

Box 1. Clinical classification of PH. Modified from [10]

1. PAH
   1.1. Idiopathic PAH
   1.2. Heritable PAH
   1.3. Drug- and toxin-induced PAH
   1.4. PAH associated with:
      1.4.1. Connective tissue disease
      1.4.2. HIV infection
      1.4.3. Portal hypertension
      1.4.4. Congenital heart disease
      1.4.5. Schistosomiasis
   1.5. PAH long-term responders to calcium channel blockers
   1.6. PAH with overt features of venous/capillaries (PVOD/PCH) involvement
   1.7. Persistent PH of the newborn syndrome
2. PH due to left heart disease
   2.1. PH due to heart failure with preserved LVEF
   2.2. PH due to heart failure with reduced LVEF
   2.3. Valvular heart disease
   2.4. Congenital/acquired cardiovascular conditions leading to post-capillary PH
3. PH due to lung diseases and/or hypoxia
   3.1. Obstructive lung disease
   3.2. Restrictive lung disease
   3.3. Other lung disease with mixed restrictive/obstructive pattern
   3.4. Hypoxia without lung disease
   3.5. Developmental lung disorders
4. PH due to pulmonary artery obstructions
   4.1. Chronic thromboembolic PH
   4.2. Other pulmonary artery obstructions
5. PH with unclear and/or multifactorial mechanisms
   5.1. Hematological disorders
   5.2. Systemic and metabolic disorders
   5.3. Others
   5.4. Complex congenital heart disease

LVEF = left ventricular ejection fraction; PAH = pulmonary arterial hypertension; PCH = pulmonary capillary hemangiomatous; PH = pulmonary hypertension; PVOD = pulmonary veno-occlusive disease
defined, as in our patient, by the following laboratory criteria [8,9]:

- Markedly reduced serum concentrations of IgG, in combination with low levels of IgA and/or IgM;
- Poor or absent response to immunizations;
- An absence of any other defined immunodeficiency state;
- Frequent respiratory infections favoring the formation of bronchiectasis.

Pulmonary hypertension (PH) is an unusual complication of CVID, with largely unknown characteristics. The underlying mechanisms have been described recently [4,6].

In many patients, the diagnosis of PH is made thanks to a variety of clinical findings and non-invasive tests. For example, a clinical diagnosis is commonly made in patients with PH due to significant left heart disease (LHD) or chronic lung disease (CLD). Conversely, some patients require hemodynamic diagnosis by right heart catheterization (RHC); e.g., patients with suspected idiopathic pulmonary arterial hypertension (PAH), few patients in group 3 PH (<5%) have severe PH (mPAP ≥35 mmHg or mPAP ≥25 mmHg and elevated right atrial pressure and/or a cardiac index <2 L/min/m²). The severity of PH appears to correlate with the severity of the underlying disorder [16].

The prevalence of group 3 PH varies depending on the underlying disease and its severity, with rates ranging from 20% to 90%. Most patients in group 3 PH have mild-to-moderate elevations in mean pulmonary artery pressure (e.g., mPAP 25 to 34 mmHg) [17] (Table II). In contrast, to patients with group 1 pulmonary arterial hypertension (PAH), few patients in group 3 PH (<5%) have severe PH (mPAP ≥35 mmHg or mPAP ≥25 mmHg and elevated right atrial pressure and/or a cardiac index <2 L/min/m²). The severity of PH appears to correlate with the severity of the underlying disorder [18].

In a recent study by Thore et al. [4], CVID-associated PH seems to be a late complication of the disease (arising in a median time of 12 years). In that court, Authors estimate that PH occurs in at least 0.37% of CVID patients, but they assume that the actual value should probably be much higher since screening for PH in CVID patients is not routinely performed due to the multifactorial nature of dyspnea in this population. This factor must be considered by physicians working in Internal Medicine, who sometimes supervise these patients if Expert Centers are far and may first suspect CVID as a new diagnosis [4].

Echocardiography is used to detect elevated pulmonary artery systolic pressures (ePASP) as well as altered right-sided ventricle structure or dysfunction and evidence of left-sided heart disease. However, the definition of mild, moderate, and severe PH on echocardiography is ill-defined (and the cut-offs are somewhat arbitrary). In addition, echocardiography can be misleading, particularly in those with advanced lung disease [11,12]. Right cardiac catheterization confirmed the presence of moderate pre-capillary pulmonary hypertension (34 mmHg) in accordance with the international classification, which includes 3 classes of severity [13-15] (Table II).

The patient’s alveolar capillary diffusion, associated with alveolar ventilation, was severely impaired (38%) and correlated, as described in the literature, with the severity of PH [16].

In our patient, the pathogenesis of PH is complex. In fact, there are pulmonary causes belonging to group 3 and lesser-known causes probably associated with the known CVID.

In 2018, our patient had undergone right heart catheterization at the University of Pavia, following the echocardiographic finding of severe pulmonary hypertension (60 mmHg).

### Table II. Pulmonary hypertension severity. Modified from [15].

<table>
<thead>
<tr>
<th>Echocardiography ePASP (mmHg)</th>
<th>Pulmonary artery catheter mPAP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild</strong></td>
<td>≥20 and &lt;40</td>
</tr>
<tr>
<td></td>
<td>≥25° and &lt;30</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>≥40 and &lt;60</td>
</tr>
<tr>
<td></td>
<td>≥30 and &lt;35</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td>≥60</td>
</tr>
<tr>
<td></td>
<td>≥35</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>≥25 and elevated RA pressure and/or</td>
</tr>
<tr>
<td></td>
<td>CI &lt;2 L/min/m²</td>
</tr>
</tbody>
</table>

*Those with mPAP between 20 and 24 mmHg are considered to have borderline elevations in PAP of uncertain significance.*

CI = cardiac index; ePASP = estimated pulmonary artery systolic pressure; mPAP = mean pulmonary artery pressure; RA = right atrial
inflammatory nature of CVID: pulmonary vascular remodeling, pulmonary parenchymal involvement, extrinsic compression by mediastinal lymphadenopathies, and portal hypertension [10].

Clinical evaluation of the patient and the rate of change over time are also indicative of prognosis. In this regard, the WHO has issued a specific classification (Table III).

By analyzing Table III, it is clear that our patient belongs to the second class. It is important to preserve the performance status as much as possible.

In the care of our patient, oxygen therapy is crucial, but respiratory physiotherapy is also important.

Not many studies have been published in the literature where the various techniques of physio-kinesiotherapy (PKT) and their efficacy in non-cystic fibrosis (CF) bronchiectasis have been evaluated. For this reason, their indication is often extrapolated from other researchs, such as those published on CF and chronic obstructive pulmonary disease (COPD) [20,21]. Some caution is always required in importing these techniques into the therapeutic plan of patients suffering from non-CF bronchiectasis, due to the pathophysiological differences between the various diseases where they have been used [22,23].

The most described PKT techniques are:

- Active cycle of breathing techniques (ACBT);
- Forced expiration techniques (FET);
- Autogenous drainage;
- Postural drainage;
- Oscillating positive expiratory pressure (OPEP);
- High-frequency chest wall oscillation (HFCWO);
- Physical exercise or pulmonary rehabilitation [23].

### CONCLUSIONS

The presence of chronic hypoxemia worsens and exacerbates the pathogenetic mechanisms of precapillary pulmonary hypertension; hence, the importance of correcting chronic hypoxemia with proper long-term oxygen therapy with adequate flow at rest, under exertion and at night.

Respiratory physiotherapy, especially if assisted, motivates the patient to remove secretions that obstruct the airways.

### Table III. Pulmonary hypertension WHO classification. Modified from [19].

<table>
<thead>
<tr>
<th>Class</th>
<th>WHO functional classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Patients with pulmonary hypertension but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea, chest pain, or heart syncope.</td>
</tr>
<tr>
<td>II</td>
<td>Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in undue fatigue or dyspnea, chest pain, or heart syncope.</td>
</tr>
<tr>
<td>III</td>
<td>Patients with pulmonary hypertension but without resulting in marked limitations of physical activity. They are comfortable at rest. Less than ordinary physical activity cause undue fatigue or dyspnea, chest pain, or heart syncope.</td>
</tr>
<tr>
<td>IV</td>
<td>Patients with pulmonary hypertension resulting in inability to carry on any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by physical activity.</td>
</tr>
</tbody>
</table>

### Key points

- The pathogenetic basis of pulmonary hypertension is varied, often multiple, and complex.
- The role of hypoxia in pulmonary hypertension is important and therefore needs to be corrected.
- Custom titration of prescribed long-term oxygen flows is critical to future patient survival.
- In the context of complex pathologies, hypoxemia should never be underestimated.

### Consent to publication

We confirm that informed consent was obtained from the patient, who has given full permission to publish this case and the accompanying images.

### Funding

This article has been published without the support of sponsors.

### Conflicts of interests

The authors declare they have no competing financial interests concerning the topics of this article.
REFERENCES


