Autoimmune PAP (aPAP) in children


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Take home message (256 characters)

In children, management of autoimmune pulmonary alveolar proteinosis is very challenging. We need to consider all treatment options, as the most effective one with best harm to benefit ratio is unknown.
**Abstract**

In childhood, a multitude of causes leads to pulmonary alveolar proteinosis (PAP), an excessive surfactant accumulation in the alveolar space limiting gas exchange. Autoantibodies against GM-CSF causing autoimmune PAP, the principle etiology in adults, are rare.

In this first series on autoimmune PAP we detail the presentation and management issues of four children.

Whereas three children presented insidiously with progressive dyspnea, one was acutely sick with suspected pneumonia. During management, one patient was hospitalized with COVID-19, non-invasively ventilated, and recovered. All treatment modalities known from adults including whole lung lavages, augmentation of GM-CSF by inhaled GM-CSF, removal of neutralizing antibody by plasmapheresis and interruption of antibody production by Rituximab were considered, however not all options were available at all sites. Inhaled GM-CSF appeared a non-invasive and comfortable therapeutic approach.

The management with best benefit to harm ratio in autoimmune PAP is unknown and specialized physicians must select the least invasive and most effective treatment. To collect this cohort in a rare condition became feasible as patients were submitted to an appropriate registry. To accelerate authorization of novel treatments for autoimmune PAP competent authorities should grant an inclusion of adolescents into trials in adults.
Introduction

Inappropriate catabolism of surfactant and consecutive filling of the alveoli defines pulmonary alveolar proteinosis (PAP). The progressive ‘occupation’ of the alveolar spaces by an excessive amount of surfactant limits gas exchange and gradually exhausts respiratory reserve, leading to respiratory failure and, if untreated, to death (1).

Granulocyte monocyte colony stimulating factor (GM-CSF) primarily drives removal of surfactant by alveolar macrophages. Whereas in adults autoantibodies against GM-CSF are the principle cause of PAP, in children this cause is rarely identified (2). Until today less than 10 cases have been published (3-9), whereas a genetically caused interruption of signal transduction of the GM-CSF receptor due to mutations in downstream α or β subunit of the receptor have been more frequently described (2).

Independently of the etiology, patients with PAP present with chronic, often dry cough, progressive dyspnea when exercising and later on at rest. Often this remains unrecognized for many months (1). In some children with PAP, particularly with GM-CSF receptor mutations, an acute presentation as a respiratory tract infection with fever or chest pain may be seen (10). Then the characteristic, however non-pathognomonic bilateral ground glass opacification with reticulation from interlobar septal thickening (“crazy paving”) on computerized tomography (CT)(Fig. 1a) needs to be differentiated. Crazy paving can be seen in a number of other diseases, including Pneumocystis pneumonia, bacterial pneumonia, lipoid pneumonia, and acute respiratory distress syndrome, including COVID-19 (11). In CTs from children with
COVID-19 crazy paving occurs in only 0.5% (adults 15-36%), ground glass opacification in 37% (adult 68-83) and consolidation in 22% (adults 33-44%) (Fig 1b) (12). For PAP, the history, a characteristic CT scan along with a viscid and milky bronchoalveolar lavage (BAL) fluid, showing a crowded background of granular cellular and acellular debris, staining positive with periodic acid-Schiff, are diagnostic. Then more than 100 different forms and causes of PAP in pediatrics need to be differentiated (2). Increased levels of neutralizing serum anti-GM-CSF auto-antibodies further differentiate and diagnose the autoimmune form of PAP, aPAP (13).

We present four children with aPAP, among them one presenting acutely during the early COVID-19 pandemics and another one experiencing COVID-19. Medical treatment of PAP was very challenging in all children and appeared most successful with inhaled GM-CSF.

Case series (Tab. 1)

All patients presented with characteristic PAP symptoms and positive GM-CSF autoantibodies. All were included into the kids-lung-register at chILD-EU management platform after written informed consent. The register study and evaluation and reporting was approved by the Ethics committee of LMU Munich (EK 111-13, 20-329).

Diagnosis was compounded in patient 1, a 14-year-old female adolescent, who came to the emergency department with the potential diagnosis of COVID-19, due to a 2-day history of temperature up to 37.9°C, progressive dyspnea, low O₂-saturation (S_{PO2}=89% at room air) and expiratory
crackles. Chest X-ray (CXR) revealed bilateral infiltrates. Diagnostics for SARS-CoV-2 were negative. As there was no response to treatment of community acquired pneumonia, further diagnostic work-up was performed and aPAP was diagnosed. On the basis of the existing Greek legislation, to initiate “off-label” rescue inhaled (i)GM-CSF therapy, the patient was registered at the National Drug Administration and her parents provided written informed consent. 250 µg GM-CSF (Sargramostim, Leukine®, Genzyme Corporation, Cambridge, MA, USA) were inhaled daily via an LC-STAR nebulizer with a manual interrupter valve connected to a PARI Turbo BOY compressor (13). The patient improved gradually and attained complete remission of respiratory failure at rest at the end of the first month of treatment. Treatment was tapered to 4 days on, 1 day off at 3 months. Four months after treatment initiation, chest CT showed a decrease in radiological findings and lung function improved with FVC (58% predicted) and DLCO (49% predicted).

Patient 2 had progressive dyspnea with exercise for 1.5 y, he had no appetite, and a weight loss of several kilogram body weight. From the diagnosis onward, he was in need of monthly whole lung lavages (WLL). Each lavage improved respiratory failure, in that the boy was able to attend school and sustain everyday life activities; however, he experienced desaturation of $S_{pO2}<90\%$ with slight exercise. Severe COVID-19 complicated his course, which rendered non-invasive ventilation and a hospital stay necessary. Treatment with inhaled GM-CSF was suggested early, however the insurance refused to cover the costs until recently, when permission for one year of treatment was granted.
**Patient 3**, aged 10 years, had no relevant preexisting conditions. 12 months prior to diagnosis, symptoms began with progressive dyspnea on exertion and a persistent dry cough following an infection with fever for 2 weeks, as well as weight loss. An asthma therapy (fluticasone/salmeterol) was started without clear effect. At the age of 10 years, she was admitted because of hypoxemia ($S_{pO2}=90\%$ at rest while breathing room air) without any signs of an infection. aPAP was diagnosed subsequently and after the first WLL, the girl no longer needed oxygen supplementation, but remained on a limited pulmonary function. Inhaled GM-CSF, started at the age of 10.3 years, led to stabilization. To facilitate improvement, two further WLL were performed.

**Patient 4** was a 15-year-old, malnourished (body mass index 14 kg/m$^2$, below 3rd percentile) boy, with no history of respiratory tract infections or environmental exposure. Four months after symptom start, he presented with acute respiratory failure (high flow oxygen FiO$_2$ 0.6-0.75). Six WLL were performed, the first one under extracorporeal membrane oxygenation (ECMO) without significant clinical improvement. To improve the poor clinical condition, the child was treated with 10 sessions of plasmapheresis followed by two doses of rituximab. Dyspnea, need of O$_2$-supply and WLLs improved and only one WLL was necessary within a period of 8 months. Currently he is on high-flow-O$_2$ (FiO$_2$=0.3) during sleep, has improved overall condition and BMI (16 kg/m$^2$).

**Discussion**
Autoimmune PAP (aPAP) is an ultra-rare condition in children and adolescents, with only few cases described worldwide; here we present the first series of four cases of pediatric aPAP and highlight in detail up-to-date management problems.

Diagnosis of aPAP is difficult and necessitates a high degree of awareness, as the disease often progresses slowly. Hallmark feature of chronic interstitial disease is desaturation upon exercise, and this should prompt referral to specialized pediatric pneumology care. The COVID-19 pandemic added another layer of complexity, as the combination of fever and ground-glass opacities on chest imaging (Fig. 1b) are compatible with SARS-CoV-2-related pneumonia at any age group (14). Thus, not only the initial diagnosis, but also an exacerbation in a patient with established PAP and residual ground glass on imaging constitutes a challenge and prompts the clinician to repeated PCR testing or considering early SARS-CoV-2 monoclonal antibody treatment.

Treatment of PAP in children is very challenging and the results are not satisfying. Due to its extreme rarity, there is no “standard treatment” and there are no consensus recommendations on how to treat pediatric PAP. The few specialized centers apply different treatments based on locally available techniques, personal expertise; experience collected in adult subjects and published reports. The cases reported here reflect this heterogeneity and are an important starting point to gauge management recommendations.

Available treatment options for aPAP include WLL; augmentation of GM-CSF by iGM-CSF or s.c.GM-CSF; removal of neutralizing ANTIBODY by
plasmapheresis and interruption of ANTIBODY production by drugs, including B-cell depleting antibodies. Lung transplant is not a real option, as recurrent disease has been described (1).

WLL is an invasive procedure taking 3 to 7 hrs of general anesthesia, often associated with post-interventional mechanical ventilation and initially sometimes requiring extracorporeal membrane oxygenation (15). In children monthly procedures sometimes over years under general anesthesia for several hours have huge psychosocial impact on the developing child, in addition to risk of medical complications, including airway injury, particularly in small infants, hypoxemia and cerebral insult from frequent usage of anesthetics (16). This technique may be used for rescue of severe respiratory failure and initially, when it is not yet clear how many whole lung lavages will be necessary or when no other treatment option is available. In milder cases lavage of all lobes by flexible bronchoscopy has been feasible (17).

Competitive binding of the disease-causing, neutralizing endogenous GM-CSF auto-antibodies by inhaled or subcutaneously applied recombinant GM-CSF is an elegant pathophysiological approach to treat aPAP and was for the first time successfully used 25 years ago (1). Aerosolized GM-CSF is most promising and supported by several clinical trials with response rates of 62%, long term treatment effects (18). A review summarized that iGM-CSF treatment was more effective than s.c.GM-CSF therapy, including a higher response rate (89% vs. 71%, p = 0.023)(19). Almost all evidence was derived in adults; however, in adolescents with aPAP similar responses to iGM-CSF are expected as shown in one of the cases reported here.
Elimination of the circulating disease-causing GM-CSF antibodies from the circulation and consecutively from affected deeper tissue compartments by plasmapheresis or similar procedures, in combination with inhibition of novel antibody production by antibodies against B- or plasma cells is rather invasive due to the necessity of a large bore central vascular access and induction of long-lasting general immunodeficiency (1).

Summarizing our experience in the management of four children as presented here, whole lung lavages were not as efficient as reported in adult patients, with a success rate of up to 70% for long lasting cure (1). In one of our patients, a very intense regimen with monthly or more frequent lavages was necessary. The techniques and volumes applied per kilogram body weight were the same as in adult subjects. Combining WLL with debilitating plasmapheresis cycles and rituximab treatment prolonged the interval between lavages, at the expense of significant immunosuppression. Inhaled GM-CSF extended its powerful therapeutic potential and safety to the clinical setting of young pediatric patients with aPAP. Clearly, iGM-CSF is the least invasive and most comfortable therapeutic approach, avoiding repetitive long-lasting anesthesia, risky procedures like whole lung lavages and plasmapheresis or long-term immunosuppression in the treatment of such young adolescents. Considering overall costs for a treatment over 3 months, iGM-CSF (Sargramostin 75 ampules) costs 26,170 €, 3 whole lung lavages with intensive care support 33,400 €.

As there is no “standard treatment” for pediatric PAP, including aPAP, it is important to consider in every single child all treatment options, as the most effective one with best harm to benefit ratio is unknown. Depending on
the presentation, specialized physicians must select the least invasive and most effective treatment; health insurances ought to cover the costs.

One major limitation of this work relates to the few cases presented of this ultra-rare condition; thus, we recommend referring all cases with pediatric PAP to an appropriate registry. In the near future, register-based observational trials may yield new insights. Lastly, competent authorities must take care to guarantee inclusion of adolescents with ultra-rare conditions into adult trials (20) to accelerate access to novel treatments.
Table 1 Presentation and treatment of 4 children with autoimmune PAP

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation (y), follow up age (y)</td>
<td>14, female, 14.7</td>
<td>14, male, 16</td>
<td>10, female, 10.5</td>
<td>15, male, 17</td>
</tr>
<tr>
<td>Previous history</td>
<td>Progressive dyspnea on exertion for 7 months, two episodes of presumptive “community acquired pneumonia” with fever, parenchymal lung infiltrates and dyspnea during the last 18 months</td>
<td>Progressive dyspnea with exercise for 1.5 y, weight loss, no appetite</td>
<td>No previous respiratory complaints. For 1 y progressive dyspnea on exertion, dry cough starting with a lower respiratory tract infection with fever over two weeks. Weight loss (3-4 kg). For 6 months inhaled steroids, long acting β-agonists.</td>
<td>No previous relevant respiratory or other symptoms. 3 months of progressive asthenia (very low weight (body mass index 15 Kg/m2; &lt;3rd percentile)), dry cough and dyspnea</td>
</tr>
<tr>
<td>Initial presentation</td>
<td>37.9°C, progressive dyspnea, SpO2 89% in ambient air at rest, 94% on 4L/min O2, 25 breaths/min, expiratory crackles</td>
<td>No fever, no infections, pale, acro-cyanosis SpO2 at rest 88%, with slight movements &lt;85%.</td>
<td>No fever, no infections, pale, tachydyspnoe, SpO2 89% at ambiente air at rest, inspiratory crackles</td>
<td>No fever, significant retractions, tachypnea, inspiratory crackles. SpO2 &lt;89%</td>
</tr>
<tr>
<td>CT scan with characteristic crazy paving pattern</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>BAL with milky appearance and cytology with acellular debris, no pathogenic organisms</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Anti-GMCSF antibody level (µg/ml) (reference: &lt; 3)</td>
<td>25.5</td>
<td>21.2</td>
<td>Positive (Berlin and Hannover, Germany; not quantified)</td>
<td>Highly positive (Cambridge, UK; not quantified)</td>
</tr>
<tr>
<td>LDH (U/ml) at diagnosis (fold upper limit)</td>
<td>1.6</td>
<td>1.3</td>
<td>0.9</td>
<td>0.5</td>
</tr>
<tr>
<td>FVC (% pred) initial / last</td>
<td>50 // 60</td>
<td>35 // 32</td>
<td>16.5 // 35</td>
<td>32 // 28</td>
</tr>
<tr>
<td>DLCO (% pred)</td>
<td>31</td>
<td>Not done</td>
<td>Not done (55.3 after first WLL)</td>
<td>20.4</td>
</tr>
<tr>
<td>SARS-CoV-2 PCR test</td>
<td>Negative</td>
<td>Severe COVID-19 at age 15.3, 6d hospitalization, dextra, 5d NIV, increased O2 need</td>
<td>Negative</td>
<td>Not done</td>
</tr>
<tr>
<td>SARS-CoV-2 serum</td>
<td>Not done</td>
<td>228 (ref &lt; 0.8)</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>antibody level (U/ml)</td>
<td>WLL number / time period</td>
<td>Inhaled GMCSF (dose, duration)</td>
<td>Plasmapheresis-scheme, rituximab – doses</td>
<td>Overall outcome of PAP</td>
</tr>
<tr>
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<tr>
<td></td>
<td>None</td>
<td>Sargramostim 250μgr daily (Leukine®) via an LC-STAR nebulizer with a manual interrupter valve connected to a PARI Turbo BOY compressor</td>
<td>Not done</td>
<td>Gradual improvement, complete remission of respiratory failure at rest at the end of the first month of treatment. Treatment was tapered to 4 days on, 1 day off at 3 months of further improvement. At four months after treatment initiation, CT of the chest demonstrated amelioration of the radiologic findings and PFTs showed an increase of FVC% predicted to 58% and DLCO% predicted to 49%.</td>
</tr>
<tr>
<td></td>
<td>13 (within 1 y)</td>
<td>Rejected by insurance, despite repetitive applications; court hearing pending</td>
<td>Not done</td>
<td>With monthly WLL just stable, deterioration to baseline before next WLL</td>
</tr>
<tr>
<td></td>
<td>3 (within 5 months)</td>
<td>Sargramostim 250μgr daily (Leukine®) via an e-flow nebulizer</td>
<td>Not done</td>
<td>Improved after first lung lavage (no oxygen dependency since then) and initiation of GM-CSF inhalation. No dyspnea at rest or low physical activity but no reconstitution of lung function since first WLL</td>
</tr>
<tr>
<td></td>
<td>6 (within 8 months) prior to RTX / plasmapheresis over 1 month, followed by 1 WLL after 8 months</td>
<td>Not available</td>
<td>10 sessions of plasmapheresis followed by two doses of rituximab 375 mg/m2/dose; clinical improvement with less dyspnea and need of oxygen</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WLL insufficiently treating respiratory failure; invasive off-label plasmapheresis and rituximab resulted in less dyspnea, need of oxygen and WLL. CT and lung function improved but did not normalized.</td>
</tr>
</tbody>
</table>
References

Fig. 1

(A) Autoimmune PAP. Computerized tomography (CT) scan of a 14 8/12 year old child with 2 days of fever and dyspnea. Note the ground glass opacities and interlobar septal thickening giving the image of non-pathognomonic “crazy paving” pattern.

(b) COVID-19 pneumonia in a 3 2/12 year old child with Trisomy 21. Note bilateral ground glass and consolidating pattern. Both children had comparable degrees of respiratory insufficiency at the time of imaging.