Case report

Autoimmune pulmonary alveolar proteinosis in an adolescent successfully treated with inhaled rhGM-CSF (molgramostim)

Marta E. Gajewska\textsuperscript{a}*, Sajitha S. Sritharan\textsuperscript{a}, Eric Santoni-Rugiu\textsuperscript{b}, Elisabeth M. Bendstrup\textsuperscript{a}

\textsuperscript{a} Department of Respiratory Diseases and Allergology, Aarhus University Hospital, Denmark
\textsuperscript{b} Department of Pathology, Copenhagen University Hospital, Denmark

ARTICLE INFO

Keywords:
Pulmonary alveolar proteinosis
Granulocyte-macrophage colony-stimulating factor
GM-CSF
Molgramostim
Inhalation therapy

ABSTRACT

Autoimmune pulmonary alveolar proteinosis (aPAP) is a rare parenchymal lung disease characterized by accumulation of surfactant in the airways with high levels of granulocyte-macrophage colony stimulating factor (GM-CSF) antibodies in blood. Disease leads to hypoxemic respiratory failure. Whole lung lavage (WLL) is considered the first line therapy, but procedure can be quite demanding, specifically for children. Recently alternative treatment options with inhaled GM-CSF have been described but no consensus about the standard treatment exists. We here describe a unique case of a 14-year-old patient who was successfully treated with WLL and subsequent inhalations with molgramostim – new recombinant human GM-CSF (rhGM-CSF).

1. Introduction

Pulmonary alveolar proteinosis (PAP) is a rare parenchymal lung disease characterized by accumulation of surfactant in the airways that leads to hypoxemic respiratory failure \cite{1–3}. There are mainly three types: hereditary, secondary and autoimmune PAP \cite{1}, where autoimmune PAP (aPAP) in adults accounts for more than 90% of the cases. The literature regarding aPAP in children is sparse and the treatment algorithms are not well documented. Whole lung lavage (WLL) is considered the golden standard \cite{4}, though alternative treatment options with inhaled granulocyte-macrophage colony stimulating factor (GM-CSF) have been described \cite{5–7}. We here describe a unique case of a 14-year-old patient who was successfully treated with WLL and subsequent inhalations with molgramostim – recombinant human GM-CSF (rhGM-CSF).

2. Case

A 14-year-old girl was referred to the Danish Center of Interstitial Lung Disease, Aarhus University Hospital for specialized treatment due to a newly diagnosed aPAP. She complained of a constant cough and dyspnea upon physical exertion. She had no weight loss, fever or recurrent infections. She had no family history of lung disease and was a never-smoker. Physical examination was normal. Pulmonary function tests revealed a forced expiratory volume in one second (FEV\textsubscript{1}) of 2.23 L (62%), forced vital capacity (FVC) of 2.64 L (70%), total lung capacity (TLC) of 72% and carbon monoxide diffusing capacity (DLCO) of 54% of predicted. Arterial gas analysis showed pO\textsubscript{2} within a normal range of 14.3 kPa. According to the classification proposed by Inoue et al. her disease severity score (DSS) was 2 (symptomatic and PaO\textsubscript{2} over 70 mmHg) \cite{2}. After evaluation of the patient's history she was treated with WLL without improvement. After the third WLL, supporting treatment with inhaled GM-SCF was therefore initiated. Firstly, sargramostim (Leukine; Sanofi-Aventis; 250 \mu g x 2 per week) was used for a short period, but when molgramostim became available in a named patient program, it was decided to change the inhalations to rhGM-CSF – molgramostim (Molgradex; Savara Pharmaceuticals). We chose the following treatment protocol: 300 \mu g daily in seven days repeated with seven days of pause. After seven months, the therapy was intensified to 300 \mu g daily. HRCT one year after the treatment did not

* Corresponding author.
E-mail address: margaj@rm.dk (M.E. Gajewska).

https://doi.org/10.1016/j.rmcr.2018.02.005
Received 23 November 2017; Received in revised form 21 February 2018; Accepted 22 February 2018
2213-0071/ © 2018 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).
Material is also positive with the periodic acid-Schi
proteinaceous cell debris of exfoliated pneumocytes in the intraalveolar material. (All pneumocytes covering the alveolar walls and in the intraalveolar macrophages. Cytokeratin staining (CK) highlights the hyperplastic type-II pneumocytes on the alveolar walls and the less extent for surfactant-B (not shown), consistent with its derivation from surfactant phospholipids and protein components. Accumulation of surfactant-A is also seen in the hyperplastic.

Fig. 2. Light microscopy of the surgical biopsy from the left lung’s lingula shows lung parenchyma containing large areas where the alveoli are totally filled with a granular proteinaceous material that is strongly eosinophilic on hematoxylin-and eosin staining (HE). The alveolar walls display diffuse moderate infiltration of lympho-histiocytic cells. The intraalveolar material is also positive with the periodic acid-Schiff stain and diastase-resistant (PAS + D), as well as strongly immunohistochemically positive for surfactant-A protein (S-A) and to a less extent for surfactant-B (not shown), consistent with its derivation from surfactant phospholipids and protein components. Accumulation of surfactant-A is also seen in the hyperplastic pneumocytes covering the alveolar walls and in the intraalveolar macrophages. Cytokeratin staining (CK) highlights the hyperplastic type-II pneumocytes on the alveolar walls and the proteinaceous cell debris of exfoliated pneumocytes in the intraalveolar material. (All figures, 100X).
expressed in E. coli, whereas sargramostim is recombinant human GM-CSF expressed in yeast and is therefore glycosylated. The amino acid sequence of molgramostim is identical to human endogenous GM-CSF as compared to sargramostim, which differs from the native protein with a substitution of leucine at position 23. Although the specific biological activity (in vitro potency) is higher for molgramostim than sargramostim, the two compounds have been used interchangeably in aPAP [20,21].

There is no approved pharmacological therapy for aPAP but inhaled GM-CSF is widely used. Molgramostim is a new recombinant GM-CSF that in the present case was beneficial and without any side effects. The current case adds to the clinical experience of inhaled molgramostim [21–23], now also expanding it into the pediatric age group.

Declarations of interest

None.

References

[1] J. Ben-Dov, M.J. Segel, Autoimmune pulmonary alveolar proteinosis: clinical course and diagnostic criteria, Autimmune. Rev. 13 (4-5) (2014 Apr-May) 513-517.
[2] V. Inoue, B.C. Trapnell, R. Tazawa, T. Arai, T. Takada, N. Hizawa, et al., Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan, Am. J. Respir. Crit. Care Med. [Internet] 177 (7) (2008 Apr 1) 752-762 [cited 2017 Sep 7] Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC209788/.
[3] T. Suzuki, B.C. Trapnell, Pulmonary alveolar proteinosis syndrome, Clin. Chest Med. [Internet] 37 (3) (2016 Sep) 431–440 [cited 2017 Jul 27] Available from http://linkinghub.elsevier.com/retrieve/pii/S0272523116004380.
[4] A. Awhab, M.S. Khan, H.A. Younes, Whole lung lavage—technical details, challenges and management of complications, J. Thorac. Dis. [Internet] 9 (6) (2017 Jun) 1697–1706 [cited 2017 Jul 27] Available from: http://jtd.amegroups.com/article-19803/11597.
[5] M.E. Wylam, R. Ten, U.B.S. Prakash, H.F. Nadrous, M.L. Clavson, P.M. Anderson, Aerosol granulocyte-macrophage colony-stimulating factor for pulmonary alveolar proteinosis, Eur. Respir. J. [Internet] 27 (3) (2006 Mar 1) 585–593 [cited 2017 Sep 7] Available from: http://erj.ersjournals.com/cgi/doi/10.1183/09031936.06.0005806.
[6] A. Price, D. Manson, E. Cutz, S. Dell, Pulmonary alveolar proteinosis associated with anti-GM-CSF antibodies in a child: successful treatment with inhaled GM-CSF, Pediatr. Pulmonol. [Internet] 41 (4) (2006 Apr) 367–370 [cited 2017 Aug 15] Available from: http://doi.wiley.com/10.1002/ppul.20347.
[7] H. Yamamoto, E. Yamaguchi, H. Agata, N. Kandatsu, T. Komatsu, S. Kawasaki, et al., A combination therapy of whole lung lavage and GM-CSF inhalation in pulmonary alveolar proteinosis, Pediatr. Pulmonol. [Internet] 43 (8) (2008 Aug) 828–830 [cited 2017 Aug 15] Available from: http://www.ncbi.nlm.nih.gov/pubmed/18618617.
[8] S.H. ROSEN, R. CASTLEMAN, A.A. LIEBOW, F.M. Enzinger, R.T.N. Hunt, Pulmonary alveolar proteinosis, N. Engl. J. Med. [Internet] 258 (23) (1958 Jun 5) 1123–1142 [cited 2017 Sep 16] Available from: http://www.nejm.org/doi/abs/10.1056/NEJM195806052582301.
[9] J.A. Whitsett, S.E. Wert, B.C. Trapnell, Genetic disorders influencing lung formation and function at birth, Spec No, Hum. Mol. Genet. [Internet] 13 (suppl_2) (2004 Oct 1) R207–R215 [cited 2017 Sep 16] Available from: https://academic.oup.com/hmg/article-lookup/doi/10.1093/hmg/ddh252.
[10] S. Alavuk Kundović, L. Popović, Congenital pulmonary alveolar proteinosis: from birth to ten-years of age, Indian J. Pediatr. 89 (9) (2017 Sep) 721–723. Available from: http://link.springer.com/article/10.1007/s10915-017-2365-6.
[11] T. Suzuki, T. Sakagami, B.K. Rubin, L.M. Nogee, R.E. Wood, S.L. Zimmerman, et al., Familial pulmonary alveolar proteinosis caused by mutations in CSF2RA, J. Exp. Med. [Internet] 205 (12) (2008 Nov 24) 2701–2710 [cited 2017 Sep 16] Available from: http://www.jem.org/lookup/doi/10.1186/jjem.20080990.
[12] U. Dräksen, R. Nishinakamura, P. Gornecke, U. Hattenhorst, L. Nogee, R. Murray, et al., Human pulmonary alveolar proteinosis associated with a defect in GM-CSF/IL-3/IL-5 receptor common beta chain expression, J. Clin. Invest. [Internet] 100 (9) (1997 Nov 1) 2211–2217 [cited 2017 Sep 16] Available from: http://www.jci.org/articles/view/11975.
[13] M. Trukajl, M. Perica, Ž. Ferocić, D. Erov, M. Navratil, G. Redžepi, et al., Successful treatment of autoimmune pulmonary alveolar proteinosis in a pediatric patient, Am. J. Case Rep. [Internet] 17 (2016 Sep 5) 641–645 [cited 2017 Sep 16] Available from: http://www.ncbi.nlm.nih.gov/pubmed/27952713.
[14] G.A. Sideris, M. Josephson, Pulmonary alveolar proteinosis and Niemann Pick disease type B: an unexpected combination, Respir. Med. Case Rep. [Internet] 19 (2016) 37–39 [cited 2017 Sep 16] Available from http://linkinghub.elsevier.com/retrieve/pii/S2213007116300533.
[15] T.R. Robinson, B.C. Trapnell, M.L. Goris, L.M. Quittrell, D.N. Cornfield, Quantitative analysis of longitudinal response to aerosolized granulocyte-macrophage colony-stimulating factor in two adolescents with autoimmune pulmonary alveolar proteinosis, Chest [Internet] 135 (3) (2009 Mar) 842–848 [cited 2017 Sep 16] Available from: http://www.ncbi.nlm.nih.gov/pubmed/19205994.
[16] J. Ramirez, R.F. Kieffer, W.C. Ball, Bronchopulmonary lavage in man, Ann. Intern. Med. [Internet] 63 (5) (1965 Nov) 819–828 [cited 2017 Sep 19] Available from: http://www.ncbi.nlm.nih.gov/pubmed/5846330.
[17] I. Campo, M. Luisetti, M. Gries, B.C. Trapnell, F. Bonella, J. Grutters, et al., Whole lung lavage therapy for pulmonary alveolar proteinosis: a global survey of current practices and procedures, Orphanet. J. Rare Dis. [Internet] 11 (1) (2016 Aug 31) 115 [cited 2017 Sep 19] Available from: http://ord.biomedcentral.com/articles/10.1186/s13023-016-0497-9.
[18] D.R. Compa, M.A. Judson, S.H. Beegle, Granulomatosis and polyangiitis followed by alveolar proteinosis in a 32-year-old woman, Chest [Internet] 141 (5) (2012 May) 848–849 [cited 2017 Sep 19] Available from: http://doi.wiley.com/10.1164/rccm.201106-1076OC.
[19] S. Leth, E. Bendstrup, H. Vestergaard, O. Hildberg, Autoimmune pulmonary alveolar proteinosis: treatment options in year 2013, Respiriology [Internet] 18 (1) (2013 Jan) 82–91 [cited 2017 Aug 15] Available from: http://doj.wiley.com/10.1111.j.1525-1576.2011.00845.x.
[20] J.F. Seymour, J.J. Pressnell, O.D. Schoch, G.H. Downie, P.M. Moore, I.R. Doyle, et al., Therapeutic efficacy of granulocyte-macrophage colony-stimulating factor in patients with idiopathic acquired alveolar proteinosis, Am. J. Respir. Crit. Care Med. 163 (2001) 524–531.
[21] K. Ohashi, A. Sato, T. Takada, T. Arai, T. Nei, Y. Kasahara, et al., Direct evidence that GM-CSF inhalation improves lung clearance in pulmonary alveolar proteinosis, Respir. Med. [Internet] 106 (2) (2012 Feb) 284–293 [cited 2017 Jul 27] Available from: http://www.ncbi.nlm.nih.gov/pubmed/22122784.
[22] R. Tazawa, E. Hamano, T. Arai, H. Ohta, O. Ishimoto, K. Uchida, et al., Granulocyte-macrophage colony-stimulating factor and lung immunity in pulmonary alveolar proteinosis, Am. J. Respir. Crit. Care Med. 171 (10) (2005 May 15) 1142–1149.
[23] Yu H. yan, X feng Sun, Y xun Wang, Z jun Xu, H. Huang, Whole lung lavage combined with Granulocyte-macrophage colony stimulating factor inhalation for an adult case of refractory pulmonary alveolar proteinosis, BMC Pulm. Med. 14 (2014 May 19) 87.