Hereditary Pulmonary Alveolar Proteinosis Secondary to Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) Alpha-Receptor Mutation

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Introduction: Pulmonary Alveolar Proteinosis (PAP) is a broad group of rare diseases that results from accumulation of pulmonary surfactants in alveolar space. Four forms of PAP are recognized in children: congenital, primary (autoimmune and hereditary), secondary, and idiopathic. Case Report: We present a 14-year-old girl with 2-month history of exercise induced dyspnea and 1-week history of nausea and vomiting who was transferred to Children’s of Alabama for worsening bilateral pneumonia and hypoxemia. She was previously diagnosed with exercise induced asthma by her pediatrician. Review of systems was positive for 8-pound weight loss and negative for fever, cough, night sweats, exposure to TB, recent travel and exposure to birds/hay. Physical examination was unremarkable. Her chest x-ray showed diffuse bilateral interstitial infiltrates. Follow-up CT scan demonstrated extensive abnormal appearance of the lungs; thickened interlobular septae and ground glass opacities in “crazy paving” pattern. Extensive laboratory workup was negative (CBC, CMP, ACE level, ESR/CRP, Immune workup, ANA, ANCA, ECHO, HIV, LDH, T SPOT, Hypersensitivity pneumonitis panel, Anti-GM-CSF ab). One month following her discharge, she showed no clinical improvement and was re-admitted to the hospital for hypoxemia and dehydration. She required supplemental oxygen and pulse dose steroid during this hospitalization. Additional diagnostic studies including bronchoscopy and lung biopsy were performed which exhibited markedly expanded alveolar spaces filled with granular, proteinaceous, PAS positive material, consistent with diagnosis of PAP. Blood test (performed by Bruce C Trapnell, Cincinnati Children’s Hospital) showed absent GM-CSF α receptor protein leading to a diagnosis of Hereditary PAP. She underwent whole lung lavage which ultimately led to marked clinical improvement and she was discharged home on room air. Discussion: GM-CSF plays an important role in alveolar macrophage maturation and surfactant clearance. The absence of this protein results in accumulation of surfactant in the alveolar spaces, leading to primary PAP. Hereditary PAP results from abnormalities in the GM-CSF receptor, either α or β subunits. The basic histopathologic characteristic of primary PAP is the accumulation of granular, PAS positive, lipoproteinaceous material within the alveoli. Alveolar septal fibrosis or inflammatory reactions are typically absent because the primary defect is in macrophage function rather than type II pneumocytes. Whole lung lavage is the only therapy that has been proven to be beneficial in patients with Hereditary PAP. Macrophage transplantation has been shown to be beneficial in mice with PAP, but is currently not clinically available for pediatric patients.