Automated Parenchymal Pattern Analysis of Treatment Responses in Pulmonary Alveolar Proteinosis

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Figure 1. Computed tomography (CT) evaluation of the therapeutic response to whole-lung lavage and inhaled granulocyte/macrophage colony-stimulating factor (GM-CSF) in a patient with autoimmune pulmonary alveolar proteinosis. (A–C) Thin-section volumetric chest CT at diagnosis (A), after 1 year of multiple high-volume whole-lung lavage procedures (B), and 4 months after completing a 1-year course of inhaled GM-CSF therapy (250 $\mu\text{g}/\text{d}$) (C). (D–F) CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Rating) software-generated images of the digital CT data represented earlier (A–C), with masking showing pulmonary alveolar proteinosis-involved lung (yellow) and normal lung (green) for one lung slice in cross-sectional view (D–F), and integrated across all CT scan slices to show pulmonary alveolar proteinosis involvement throughout the lungs in a coronal view (G–I).

A 48-year-old woman presented with progressive dyspnea of insidious onset, nonproductive cough, and diffuse, bilateral infiltrates on chest radiograph. Oral antibiotic therapy was initiated for a presumptive diagnosis of pneumonia with no improvement. Computed tomography (CT) of the chest revealed bilateral, diffuse, ground-glass opacification and septal thickening (Figure 1A). A serum granulocyte/macrophage colony-stimulating factor (GM-CSF) autoantibody test measured at our center was abnormal (77 $\mu\text{g}/\text{ml}$; normal, <5.0 $\mu\text{g}/\text{ml}$ [1]), establishing a diagnosis of autoimmune pulmonary alveolar proteinosis (aPAP) (2). High-volume whole-lung lavage therapy was performed three times over the course of 1 year (>80 L of lavage total), with minimal effect on symptoms or radiographic abnormalities (Figure 1B). Subsequently, inhaled GM-CSF therapy was initiated and resulted in complete resolution of symptoms, normalization of the DL_{CO} (64% $\rightarrow$ 101% of predicted), and marked radiographic improvement (Figure 1C).

Automated lung parenchymal pattern analysis of the digital CT data (3) was used to quantify the therapeutic response (Figures 1D–I), revealing minimal change (61% $\rightarrow$ 59%) in the extent of lung affected by aPAP after

1 year of whole-lung lavage therapy and marked improvement (59% $\rightarrow$ 3%) after 1 year of inhaled GM-CSF therapy (Figure 2). Recently, CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Rating) software was validated for quantitative assessment of fibrosing lung disease in patients with idiopathic pulmonary fibrosis (4) and for identification of functional patterns of obstruction and restriction in patients with hypersensitivity pneumonitis (5).

Figure 2. Relative therapeutic responses to whole-lung lavage and inhaled granulocyte/macrophage colony-stimulating factor (GM-CSF) in a patient with autoimmune pulmonary alveolar proteinosis measured using CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Rating) software. Digital chest computed tomography data (represented in Figure 1) were analyzed to identify and quantify the volume of lung (measured in numbers of voxels) categorized by CALIPER as falling into one of eight radiological parenchymal pattern categories (normal lung; mild-, moderate-, and marked-gas trapping; ground-glass opacification; reticular pattern; honeycombing; and pulmonary vessels: pulmonary arteries and veins, excluding vessels at the lung hilum), using an unsupervised clustering algorithm. Volumes for all parenchymal pattern categories were converted to percentages, using the total lung volume, which was also measured by CALIPER. (A) Glyphs showing categorical lung parenchymal pattern analysis of the entirety of both lungs represented graphically as right and left upper, middle, and lower zones (RU, LU, RM, LM, RL, and LL, respectively). Lung affected by pulmonary alveolar proteinosis (yellow) was calculated as the percentage of lung corresponding to CALIPER categories “ground-glass opacification” and “reticular densities.” Uninvolved lung (green) was calculated as the percentage of lung corresponding to the CALIPER category “normal.” (B) Histogram of the CALIPER results shown in A.

These results highlight the approach to diagnosis of aPAP, the relative therapeutic efficacy of whole-lung lavage and inhaled GM-CSF in this patient, and the utility of automated lung parenchymal pattern analysis as an outcome measure to objectively quantify disease burden in patients with aPAP. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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