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CHEST

A 51-Year-Old Woman With Interstitial Lung Disease and Subsequent COVID-19 Presenting With Worsening Dyspnea

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CASE PRESENTATION: A 51-year-old Puerto Rican woman, with a known but inconclusive diagnosis of interstitial lung disease (ILD) since 2002 and recent moderate COVID-19, is now presenting with subacute worsening dyspnea on exertion. The patient had sporadic medical care over the years for her ILD (Table 1). Prior workup included chest CT imaging with a "crazy-paving" pattern of lung disease, as defined by ground-glass opacity with superimposed interlobular septal thickening and visible intralobular lines. Bronchoscopy showed normal airway examination, and BAL revealed clear fluid with foamy macrophages and negative cultures. Video-assisted thoracoscopic surgery and transbronchial biopsy specimens both showed foamy macrophages. Results of pulmonary function testing (PFT) revealed an isolated gas transfer defect on diffusing capacity of the lungs for carbon monoxide (D_{LCO}). She had lived with mild yet nonprogressive functional impairment and stable exercise intolerance over these years. She was then hospitalized for COVID-19 in August 2020 and for recurrent shortness of breath in September 2020. She now presented 4 months following her September 2020 hospitalization.

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Physical Examination Findings

On examination, the patient's vital signs were normal except for an oxygen saturation of 83% while breathing ambient air and 94% on 3 L/min of nasal cannula. Cardiovascular, pulmonary, abdominal, dermatologic, and neurologic examinations were normal except for bibasilar rales and hepatosplenomegaly. Pertinent negative results included absence of skin findings such as petechiae and digital clubbing.

Diagnostic Studies

Basic laboratory studies revealed normal complete blood counts and no significant abnormalities, aside from mild liver function abnormality (aspartate aminotransferase, 72 U/L; alanine aminotransferase, 55 U/L). Microbiologic workup showed negative blood and respiratory culture results for any bacterial, virus, fungus, or mycobacterium, and normal (1→3)-β-D-glucan and galactomannan levels.

Chest radiograph showed persistent diffuse, bilateral reticulonodular opacities in a lower lung distribution (Fig 1). CT chest scan showed marked improvement in ground-glass opacities but persistent interlobular and intralobular septal thickening and mild bronchiectasis (Fig 2), compared with prior imaging from September 2020.

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TABLE 1] Timeline of Patient's Diagnostic Evaluation and Investigative Data

Diagnostic Test	2002	2009	2016	August 2020	September 2020
CT scan/CTA of chest (impressions)	Diffuse ground-glass opacities in bases suggestive of a "crazy-paving" pattern		Diffuse bibasilar predominant interstitial septal thickening that transitions to confluent ground-glass opacification at lung bases	Diffuse "crazy-paving" pattern, mild bronchiectasis in lower lobes, increased ground-glass opacities in perihilar/mid-lung	Progressive diffuse interlobar septal thickening with worsening superimposed ground-glass opacities compared with August 2020
Pulmonary function testing		FVC 3.47 L, 89% FEV_1 2.56 L, 80% FEV_1/FVC 74 D_{LCO} 10.2, 41% mL/(min • mm Hg) No obstruction Severe gas transfer defect	FVC 2.98 L, 80% FEV_1 2.23 L, 76% FEV_1/FVC 75 D_{LCO} 12.9, 55% mL/(min • mm Hg) No obstruction Moderate gas transfer defect		
Bronchoscopy			BAL with (foamy) macrophages 34%, neutrophils 30%, lymphocytes 18%		
Histology	VATS biopsy: Massive interstitial and airspace accumulations of foamy macrophages		TBBX: Mild chronic inflammation and marked accumulation of foamy macrophages		

CTA = CT angiography; D_{LCO} = diffusing capacity of the lungs for carbon monoxide; TBBX = transbronchial biopsies; VATS = video-assisted thoracoscopic surgery.

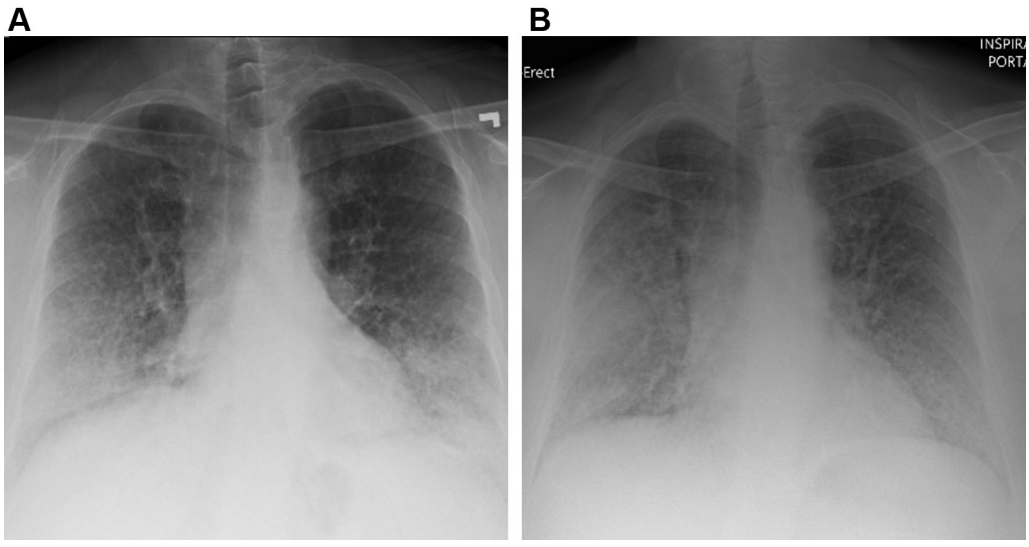

Figure 1 – *Chest radiograph (CXR). A, Anteroposterior CXR from September 2020 showing diffuse, bilateral reticulonodular opacities in a lower lung distribution. B, Anteroposterior CXR from current presentation showing persistent diffuse ill-defined reticulonodular opacities.*

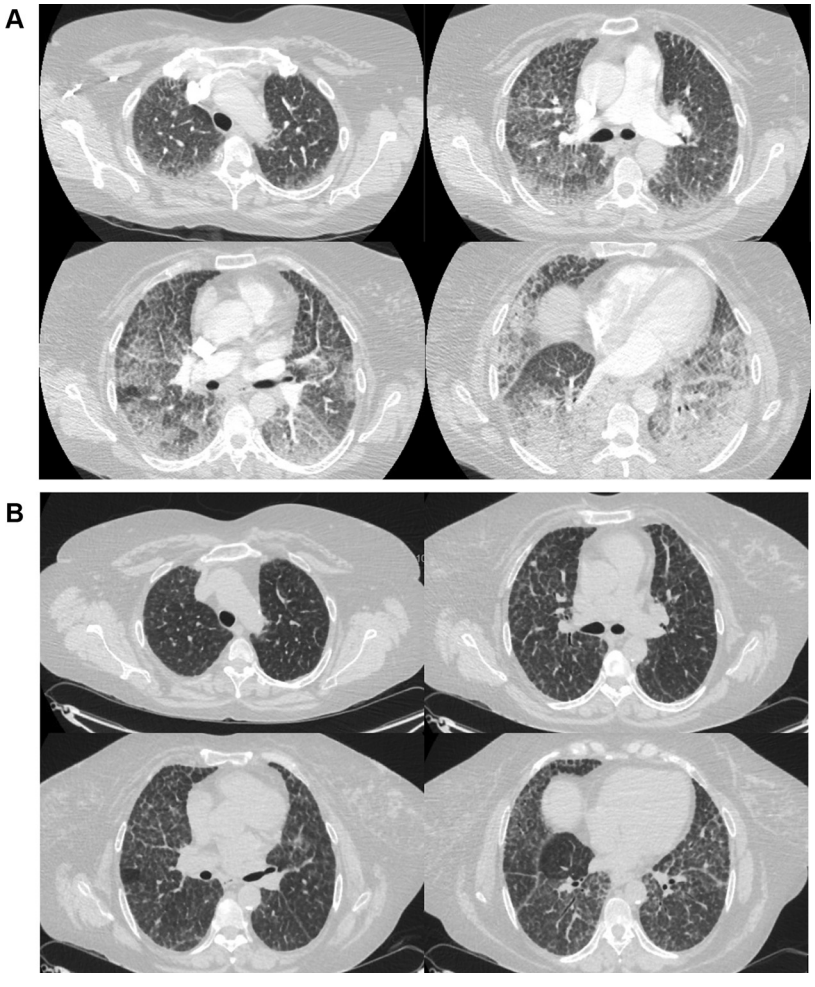

Figure 2 – *Chest CT angiography/CT imaging. A, Axial CT angiography images of the chest from September 2020 showing moderate to severe diffuse interlobular and intralobular septal thickening predominantly within the mid to lower lungs along with significant superimposed ground-glass opacities. B, Axial CT images of the chest from current presentation showing persistent interlobular and intralobular septal thickening but with marked improvement in ground-glass opacities.*

Bronchoscopy showed normal airways. BAL revealed clear fluid with a neutrophilic cellular pattern and negative culture findings. Transbronchial biopsy specimens showed mild chronic inflammation and marked accumulation of finely vacuolated foamy macrophages, similar to prior biopsy findings (Fig 3).

On extensive review of the medical record for historical data, positive findings included mild dyslipidemia (low-density lipoprotein, 171 mg/dL; high-density lipoprotein, 25 mg/dL; total cholesterol, 220 mg/dL) and a prior CT scan report from 2017 with incidental mild hepatosplenomegaly.

Leukocyte acid sphingomyelinase (ASM) enzyme assay was sent and found to be deficient at 0.14 nmol/h/mg protein (reference range, 0.41-5.87 nmol/h/mg protein).

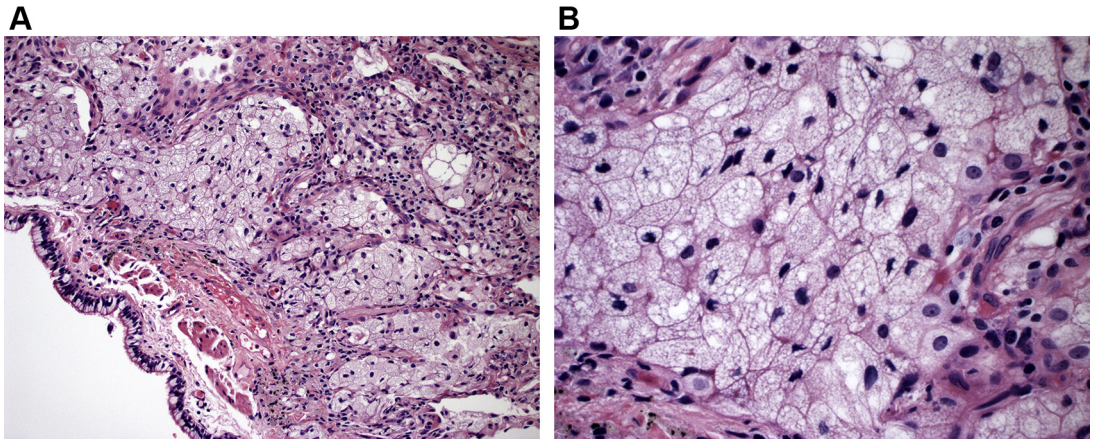

Figure 3 – *Transbronchial biopsy specimen of the lung. A, Transbronchial biopsy specimen showing alveolar spaces filled with vacuolated macrophages. The alveolar architecture is preserved. Although reported in some cases, the vacuolated cells do not involve the bronchial epithelium or interstitium in this sample (hematoxylin-eosin, ×200). B, The intra-alveolar macrophages contain fine vacuoles of roughly equal size, resembling those of endogenous lipid/postobstructive pneumonia. Ziehl-Neelsen and Grocott methenamine silver stains were negative for microorganisms (hematoxylin-eosin, ×600).*

What is the diagnosis?

Diagnosis: Acid sphingomyelinase deficiency (ASMD), formerly Niemann-Pick disease type B

Discussion

The CT scan finding of "crazy-paving" occurs from filling of airspaces with fluid, cells, or other material giving a characteristic ground-glass appearance, whereas the linear deposition of material within the airspaces at the borders of the acini indicate the features of interlobar and intralobular septal thickening. This radiographic finding has a broad differential (Table 2). Histopathology can be helpful in elucidating the etiology; however, a biopsy finding of foamy macrophages is also relatively nonspecific (Table 3). Taken together, these findings broaden the differential to include diffuse interstitial pneumonias, lipid pneumonias, drug reactions, or deposition disorders. Clinical history-taking is essential to rule out associated exposures.

Lysosomal storage disorders (LSDs) are a group of inherited metabolic disorders caused by deficiencies of lysosomal enzymes that normally function to break down macromolecules, including sphingolipids, mucopolysaccharides, and glycoproteins. The inability to break down these substrates leads to their accumulation within lysosomes of various tissues. These compounds can accumulate in multiple organs, including the lung. Alveolar involvement manifesting as ILD can be seen in four LSDs: Fabry, Gaucher, ASMD, and mucopolysaccharidoses/mucolipidosis. Of these, ASMD is the most common.

The eponym for ASMD, commonly known as Niemann-Pick disease (NPD) type A and B, refers to patients who present with variable phenotypes but share a deficiency of the same lysosomal enzyme (ASM) due to loss-of-function mutations in the sphingomyelin phosphodiesterase 1 (*SMPD1*) gene. Patients with infantile neurovisceral ASMD (NPD type A) present with hepatosplenomegaly and profound neurologic devastation, with a life expectancy of 2 to 3 years. Patients with chronic neurovisceral (NPD type A/B) and chronic visceral (NPD type B) ASMD have a less severe, later-onset presentation with more variable phenotype, lending themselves to diagnostic challenges.

At least 185 mutations have been identified as causing ASMD, which leads to the broad spectrum of disease severity. In a subset of patients, mutation analysis can assist with prediction of the phenotypic severity, but in most patients, genotype-phenotype correlations are unknown. Measurement of residual ASM activity in leukocytes or cultured skin fibroblasts also cannot inform about phenotypic severity. Thus, predicting phenotypic outcomes in newly diagnosed patients remains an important challenge.

ASMD is a rare autosomal recessive inherited disorder with a prevalence of 0.5 in 100,000. Clinical presentation is highly variable and can affect many organ systems. Splenomegaly (> 90%) is the cardinal manifestation and most common presenting sign by which patients are diagnosed. Pulmonary involvement is the next most common (80%-98%) and presents as ILD; this is further complicated by recurrent respiratory infections with progressive loss of pulmonary function and is ultimately a leading cause of death. Liver involvement (50%-74%) presents as mild transaminitis, although fibrosis and cirrhosis can be seen. Cardiac disease manifests as atherogenic lipid profiles (46%-74%), which may increase the risk for coronary artery or valvular diseases. Neurologic involvement is less common (13%-30%) and can range from mild hypotonia to severe loss of motor or cognitive function. Finally, bone marrow involvement can present with cytopenias, and skeletal involvement can present with osteopenia, osteoporosis, or pathologic fractures.

Pulmonary manifestations in ASMD have been further studied in a cross-sectional survey of 53 patients, in which 98% had evidence of at least some degree of ILD on chest imaging. Supportive features in ASMD include PFT with normal spirometry, normal or restrictive lung volumes, and reduced D_{LCO}. Chest imaging may reveal patterns of "crazy-paving," cysts, and/or centrilobular nodular opacities. Histopathology is notable for prominent vacuolated foamy macrophages. Electron microscopy shows macrophages filled with lysosomes containing lamellar bodies. Although other disorders such as Gaucher disease are often considered, these macrophages are histologically different and, rather than appearing vacuolated, contain finely fibrillary cytoplasm often described as resembling "crinkled tissue paper."

The diagnosis of ASMD is challenging and requires a high index of suspicion as clinical presentations are highly variable. Initial workup includes quantification of ASM. Deficient enzyme activity should prompt further genetic testing with sequencing of the *SMPD1* gene.

ASMD is a life-threatening disease with significant morbidity and mortality. In the largest and longest longitudinal natural history study to date, 103 patients

TABLE 2] Differential Diagnosis of Radiographic Crazy-Paving Pattern

Infections
Bacterial
Mycoplasma pneumoniae
Fungal
Pneumocystis jirovecii
Viral
COVID-19
Malignancy
Lymphangitic carcinomatosis
Mucinous adenocarcinoma
Rheumatologic
Mixed connective tissue disease
Pulmonary hemorrhagic syndrome
Interstitial lung disease
Eosinophilic pneumonitis
Lipid pneumonia
Nonspecific interstitial pneumonitis
Organizing pneumonia
Inflammatory
Acute interstitial pneumonia
Acute respiratory distress syndrome
Others
Pulmonary alveolar proteinosis
Pulmonary edema

with chronic visceral ASMD were followed up over 20 years. Eighteen patients died with a median age of 17 years and age range of 2 to 72 years. Significant morbidities seen included neurologic disease (12.6%), liver failure or cirrhosis (8.7%), coronary artery or valvular heart disease (8.7%), bleeding disorders (6.8%), and oxygen-dependent pulmonary disease (3.9%). The most common cause of death was pneumonia (27.8%), followed by liver failure, bleeding, and bone marrow transplant complications (16.7% each).

Until recently, treatment options for ASMD were limited. Initial treatment attempts were limited to case reports and included hematopoietic stem cell transplantation, lung transplantation, and whole lung lavage. Hematopoietic stem cell transplantation was found to reverse pulmonary manifestations and improve GI symptoms but had no effect on neurologic outcomes, and the procedure was complicated by graft-versus-host disease and infections. Lung transplantation has been successful in younger patients with minimal comorbidities; however, long-term outcomes are lacking. Whole lung lavage was described in a case report with mild improvement on PFT and chest radiograph.

TABLE 3] Differential Diagnosis of Intra-Alveolar Foamy Macrophages on Lung Histology

Secondary to airway obstruction (so-called endogenous lipid pneumonia)
Drug reaction
Amiodarone
Metabolic disorders
Infection

The first disease-modifying treatment for ASMD is an enzyme replacement therapy, olipudase alfa (recombinant human ASM). A phase II/III, multicenter, randomized, double-blinded trial of olipudase alfa vs placebo was conducted in 36 patients over 52 weeks, with preliminary findings showing favorable results. Both primary end points were met with significantly reduced spleen volume by 39.5% compared with a 0.5% increase in the placebo arm and significantly improved lung function (D_{LCO}) by 22% from baseline compared with 3% in the placebo arm. Based on these and prior results, the US Food and Drug Administration granted Breakthrough Therapy designation to expedite development of olipudase alfa.

Clinical Course

The patient's lung histology consistently revealed alveolar tissue with marked intra-alveolar accumulation of macrophages with a vacuolated appearance. The vacuoles were of relatively uniform size, as is typically seen in postobstructive changes (so-called endogenous lipid pneumonia) or secondary to amiodarone use; however, this did not fit with the clinical history or physiologic findings. Such macrophages have also been reported in metabolic disorders.

This constellation of findings (marked intra-alveolar foamy macrophages on biopsy sample in an adult patient with ILD, dyslipidemia, and hepatosplenomegaly) raised the concern for a form of LSD. Initial tests revealed deficient leukocyte ASM activity consistent with the diagnosis of acid sphingomyelinase deficiency (ASMD), prompting referral to a lysosomal storage disease program. Genetic testing revealed homozygosity for a pathogenic variant, c.1426C>T (p.Arg476Trp), in *SMPD1*.

As part of the management of patients with ASMD, platelet counts, hepatic function, and lipid panels were monitored. Transient elastography of the liver was

compatible with a fibrosis score of F2 and severe steatosis. Bone densitometry showed low bone mineral density, with a T-score of –2.3 for the lumbar spine. Echocardiogram was normal, and CT imaging of coronary arteries showed a coronary artery calcium score of 16 (92nd percentile). Rosuvastatin was started. Given multisystemic involvement, an application for compassionate use of olipudase alfa was granted investigational review board approval, with treatment recently initiated.

This case presented a diagnostic challenge due to the atypical presentation in an adult with predominant ILD coupled with the misconception that LSDs are disorders of childhood, as well as concomitant overlying COVID-19.

Clinical Pearls

1. *The differential for an ILD with crazy-paving on imaging and foamy macrophages on biopsy are nonspecific and include diffuse interstitial pneumonias, lipid pneumonias, drug reactions, or deposition disorders.*
2. *LSDs should be considered in an adult without relevant exposures who has an ILD with crazy-paving on imaging and excessive foamy macrophages on histology, with extrapulmonary findings of hepatosplenomegaly, dyslipidemia, or thrombocytopenia.*
3. *Diagnosis of LSDs, such as ASMD, can be expedited and screened with a blood test specific for the relevant enzyme activity (in this case, leukocyte ASM).*
4. *Therapeutic options in ASMD were limited to case reports of hematopoietic stem cell transplant, lung transplant, and whole lung lavage; however, enzyme replacement therapy with olipudase alfa has now changed the therapeutic landscape. Early referral to a specialized genetics program is also recommended.*

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Suggested Readings

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