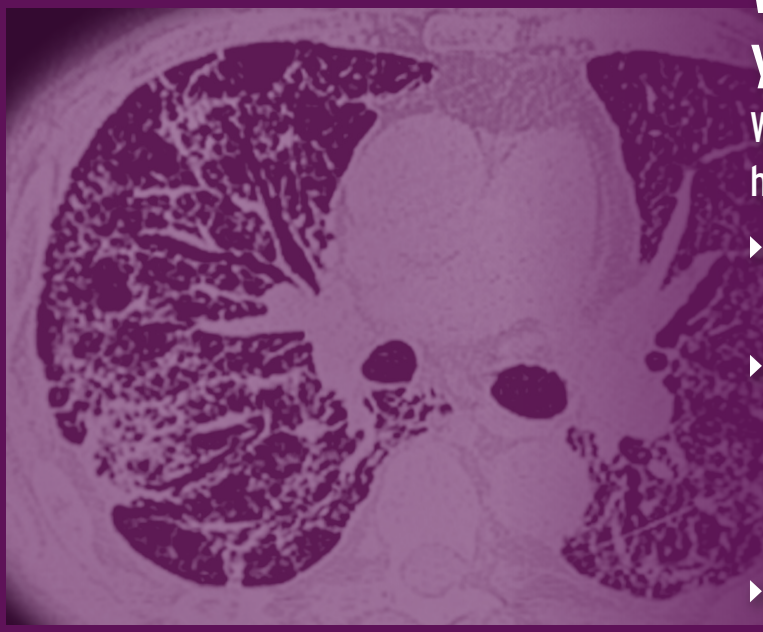
Diffuse Interlobular Septal Thickening in a Patient Less Than 40 Years Old



What's in your differential?

What would you expect if you had a patient exhibiting:

- **Diffuse interlobular septal thickening**
- **Sea-blue histiocytes** accounting for the majority of alveolar macrophages identified in BAL fluid analysis
- **Hepatosplenomegaly**
- **Thrombocytopenia**

It's not what you think...

Pulmonologists can play a critical role in the early diagnosis of ASMD

ASMD, historically known as Niemann-Pick disease types A, A/B, and B, is a progressive and often life-threatening genetic disease.[1]

BAL=bronchoalveolar lavage.

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ASMD
ACID SPHINGOMYELINASE DEFICIENCY

PULMONOLOGISTS ARE ON THE FOREFRONT OF DIAGNOSING ASMD

Cryptogenic ILD? Multisystemic involvement? It could be ASMD

- **ASMD, caused by a deficiency in the enzyme acid sphingomyelinase (ASM),** is a progressive, multisystemic genetic disease that can lead to shortened life span in both children and adults[1,2]
- **ASMD symptoms can impact the lungs, liver, and spleen, as well as the hematologic system. Some types of ASMD can also affect the neurological system[1,2]**
- **The 3 subtypes of ASMD, type A, type A/B, and type B, have variable onset, presentation, and impacts on life expectancy. Regardless of type, ASMD can lead to lifelong multisystemic complications and uncertainty for patients[2]**

Identify signs and symptoms to enable early diagnosis

Percentage of patients who experience hallmark signs and symptoms of ASMD[1,3]*

Splenomegaly	Hepatomegaly	Interstitial lung disease	Thrombocytopenia	Gastrointestinal issues†
>90%	>70%	>80%	>50%	>75%

*Symptom prevalence data for splenomegaly, hepatomegaly, interstitial lung disease, and thrombocytopenia are only for patients with ASMD type B.

†Symptom prevalence data for gastrointestinal issues are for patients with all ASMD types.

Pulmonologists can play a key role in suspecting and diagnosing ASMD:
Early diagnosis is imperative for initiating symptom management and family screening[2]

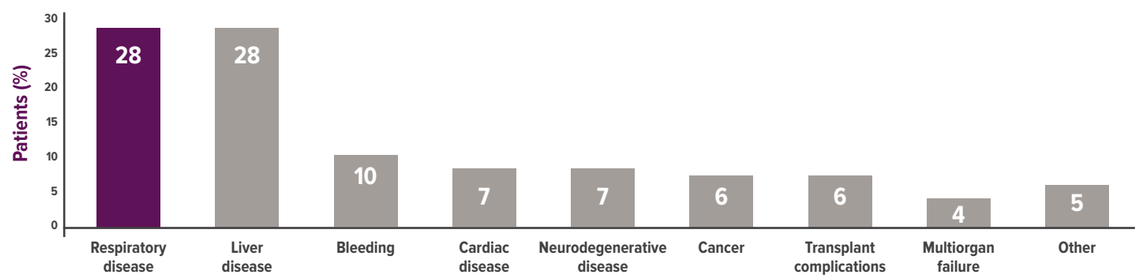
ILD=interstitial lung disease.

RESPIRATORY DISEASE: A LEADING CAUSE OF DEATH IN ASMD[4]

Patients with ASMD can experience significant morbidity and early mortality[5]

By age 35, ASMD type B patients have **~30% reduced survival probability** compared to the general US population‡

Primary causes of death in patients with ASMD types A/B and B[4]



Cassiman D, et al. *Mol Genet Metab*. 2016;118(3):206-213.

Based on a retrospective global study of 85 patients with ASMD that evaluated the causes of death and disease-related morbidity among patients with ASMD types A/B (n=27) and B (n=58). Data for 85 patients who died (n=78) or received liver transplant (n=7) were collected by treating physicians (n=27) or abstracted from previously published case studies (n=58).[4]

Know the pulmonary signs

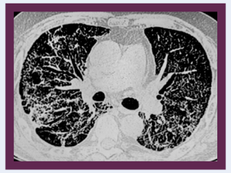
ILD§ is a hallmark sign of ASMD[1]

Interstitial lung disease
>80%

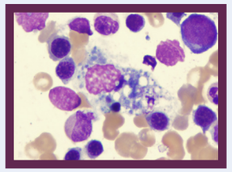
ASMD patients may also present with additional pulmonary signs and symptoms including:

- Frequent respiratory infection (including pneumonia)[1]
- Shortness of breath[6]
- Restrictive pattern on pulmonary function test[2]
- Pulmonary hypertension[3]

ILD associated with ASMD can lead to progressive deterioration of pulmonary function



Lipid-laden macrophages often accumulate in the intra-alveolar space, and typical radiologic findings include[7]:
- Interlobular septal thickening
- Crazy paving
- Ground-glass opacities



BAL fluid analysis indicating overwhelming presence of sea-blue histiocytes is another distinctive manifestation that may suggest ASMD.[7]

‡Data extrapolated from a Kaplan-Meier curve generated in an 11-year natural history study that evaluated morbidity and mortality in 59 patients with ASMD type B. At entry, 30 patients were in the pediatric age group (<18 years of age) and 29 patients were adults (≥18 years of age). There were 9 deaths during the follow-up period. Reduction in survival probability is absolute, not relative. US general population as of 2017.[5]
§ILD is identified through chest radiography and HRCT.[6]
HRCT=high-resolution computed tomography.

ASMD SIGNS AND SYMPTOMS OFTEN OVERLAP WITH OTHER LUNG DISEASES

ASMD patients can experience diagnostic delays of ~5 YEARS[6]

Phenotypic overlap with other pulmonary conditions often leads to diagnostic delays[2]

Pulmonary manifestations of ASMD may mimic[1,2,7-12]:

- Pulmonary alveolar proteinosis (PAP)
- Common variable immunodeficiency (CVID)
- Pulmonary veno-occlusive disease (PVOD)
- Connective tissue disease (CTD)
- Telomeropathies
- Pulmonary edema and hypertension
- LAM and lymphangitic malignancy
- Pneumonia, LIP, and other respiratory infections
- Cystic fibrosis

Because of the multisystemic nature of ASMD, it is also confused with other conditions including[2,13,14]:

- Acute lymphoblastic leukemia
- Non-Hodgkin lymphoma
- Chronic hepatitis B
- Congestive heart failure

LAM=lymphangioleiomyomatosis; LIP=lymphoid interstitial pneumonia.

IS ASMD PRESENTING IN YOUR PRACTICE?

Missed diagnoses are common. Your differential could make a difference[2,6]

Differential considerations in ASMD

Rule out other causes of pulmonary dysfunction[1,2,8-11,15]:

- CVID
- PAP
- Lymphatic anomalies
- CTD
- Telomeropathy
- Family history of
  - ILD
  - Aplastic anemia
  - Early graying
  - Other storage disorders
- Infection
- Malignancy
- Liver disease
- Congestive heart failure
- Hematologic disease
- Advanced pulmonary fibrosis/honeycombing

Early detection is the first step to prompt diagnosis and symptom management[2]

UNEXPLAINED ILD?
IT COULD BE ASMD. TEST TO KNOW

Diagnostic considerations for patients who may be presenting with ASMD

Alone, these signs may appear isolated, but considered together they may point to ASMD

Presentation of cryptogenic ILD suggestive of ASMD[1,3,7,16]

HRCT features

- Interlobular septal thickening
- Crazy paving
- Splenomegaly and hepatomegaly
- Ground-glass opacities

Pathology features (cryobiopsy/ VATS biopsy, BAL)*

- Foamy macrophages/sea-blue histiocytes
- Foamy epithelial cells

Other signs and symptoms suggestive of ASMD[1,2]

Infants and children

- Thrombocytopenia
- Cherry-red maculae
- Developmental delay
- Hypotonia
- Low HDL-C
- Easy bruising/bleeding

After childhood

- Thrombocytopenia
- Low HDL-C
- Pathologic fractures
- Bruising/bleeding

Age <40 years

- Cryptogenic ILD features listed above

Testing early for ASMD when you see pulmonary manifestations is crucial for symptom management. **Pulmonologists can play a critical role in enabling accurate diagnosis[2]**

*Possibly avoid biopsies if there are alternatives for diagnosis (due to bleeding risk of patients with platelet dysfunction).[1]
HDL-C=high-density lipoprotein cholesterol; VATS=video-assisted thoracoscopic surgery.

TAKE THE STEP TOWARD AN ACCURATE DIAGNOSIS

Suspect ASMD? Diagnostic testing is simple[2]

Perform an ASM biochemical enzyme assay on isolated peripheral blood leukocytes, dried blood spots (DBS), or skin fibroblasts†

↓

Low residual ASM activity

↓

ASMD diagnosis confirmed

†Limitations of DBS testing include the potential effects of anemia and recent transfusions on results. Skin fibroblasts or *SMPD1* gene sequencing can be used in equivocal cases.

APRIL
Living with ASMD type B

Additional diagnostic confirmation can be achieved using molecular genetic testing[2]

An accurate ASMD diagnosis can enable early symptom management efforts from a multidisciplinary care team before disease progression becomes severe[2]

Cryptogenic ILD?
Diffuse septal thickening?
Hepatosplenomegaly?

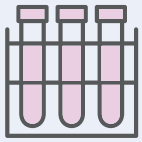
IT COULD BE ASMD

ASMD, historically known as Niemann-Pick disease types A, A/B, and B, is a multisystemic disease marked by pulmonary dysfunction that can lead to significant morbidity and early mortality[1]

Pulmonologists can make a difference

- Respiratory disease is a leading cause of mortality in ASMD[4]
- Know the hallmark signs and symptoms of ASMD that affect both children and adults[1]
  - Hepatomegaly
  - Splenomegaly
  - Interstitial lung disease
  - Thrombocytopenia

Include ASMD in your differential to enable early diagnosis and symptom management[2]



SUSPECT ASMD? TEST TO KNOW

Diagnostic testing is simple—confirm a diagnosis of ASMD with an ASM biochemical enzyme assay[2]

Find more information on ASMD and testing at **ASMDfacts.com/HCP**

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