GROUPE HOSPITALIER DIACONESSES CROIX SAINT SIMON

centre de référence maladies rares

Centre de Référence des Maladies Lysosomales

DU Maladies systémiques : Maladies Lysosomales

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Centre de Référence Maladies Lysosomales

UMRS 974, UPMC - INSERM

APMF Association des Patients de la Maladie de Fabry

Inserm

VAINCRE LES MALADIES LYSOSOMALES — RARE MAIS PAS SEUL !

CEMI Collège national des Enseignants de Médecine Interne

12 Avril 2019

Disclosure

- Travel grants and speaker honoraria from:
  - Amicus
  - Genzyme/Sanofi
  - Shire

Objectifs pédagogiques

- Connaître les principales maladies lysosomales
- Connaître leur **mode de transmission**
- Connaître leurs principaux **symptômes d'appel**

- Connaître la **démarche diagnostique** permettant d'aboutir au diagnostic de ces maladies : dosages biochimiques, analyses génétiques
- Différencier les maladies « macrophagiques » et « endothéliales »
- Reconnaitre les signes d'appel des mucopolysaccharidoses

- Connaître les **traitements** permettant de prendre en charge les patients atteints de maladies de Gaucher et de Fabry

- Maladie génétique : **un patient = une famille**

« Surcharge lysosomale »

- Fabry
- **Gaucher**
- **Niemann-Pick B**

Maladie de Gaucher type 1

- AR
- Fatigue
- Hépato-splénomégalie
- Thrombopénie
- Atteintes osseuses

- Enzymothérapie
  depuis 1991

- Y penser !!!

ASMD
ou
Niemann-Pick B

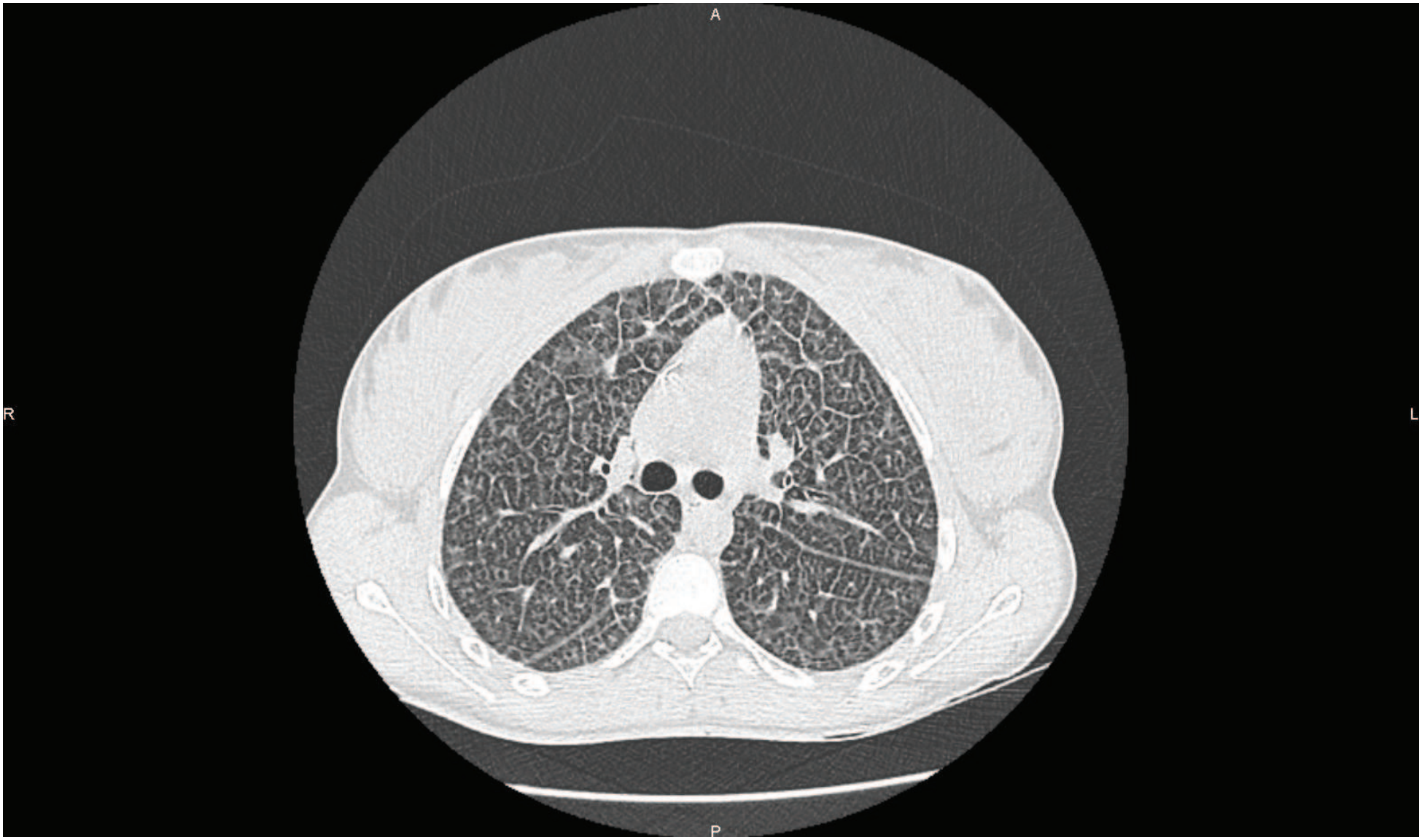
Emergency unit of our hospital

Abdominal pain

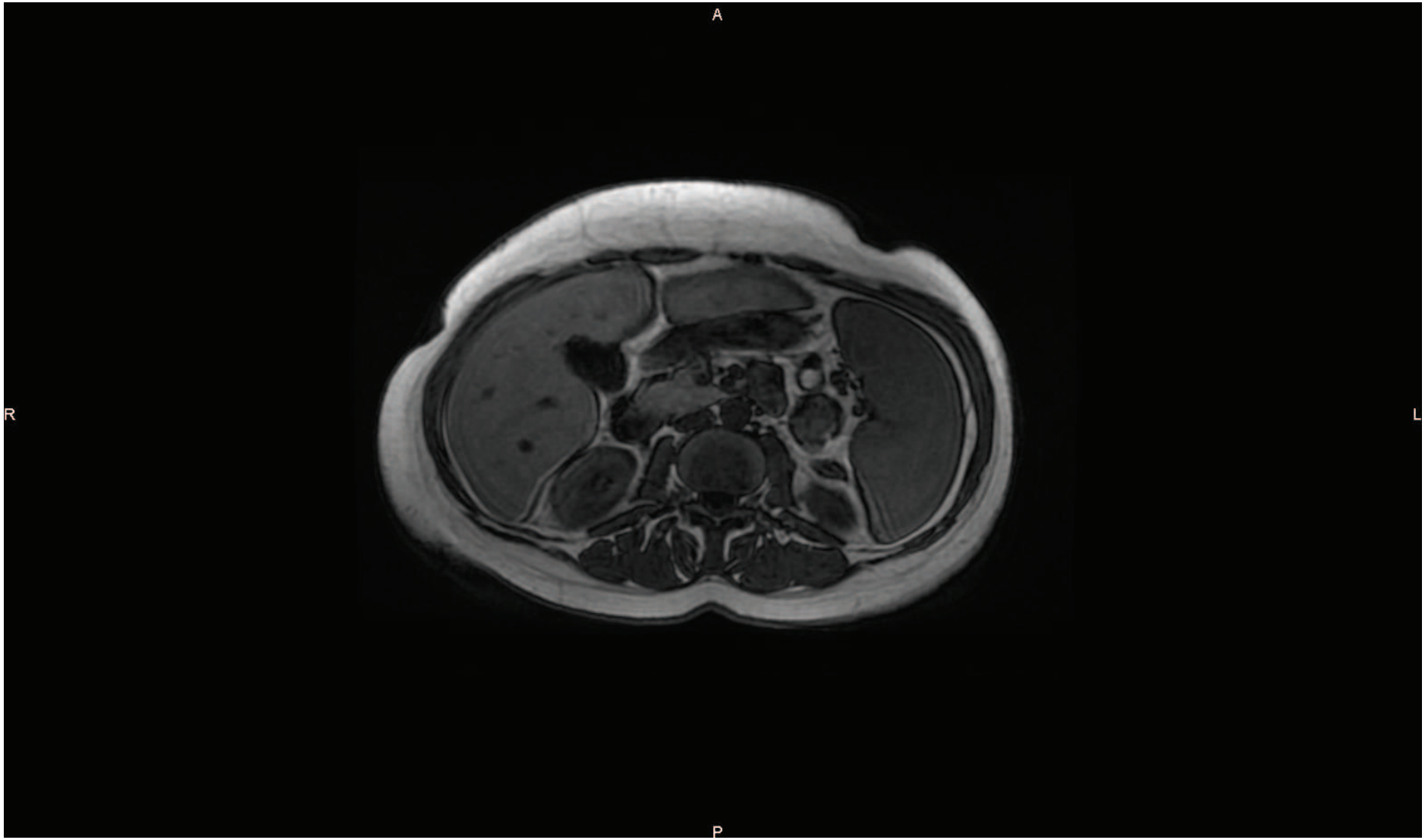
- 34-year-old female patient, originating from Tunisia
- Recurrent pain in the left part of the abdomen
- Crackles (lung auscultation)
- Liver < SPLEEN enlargement

- Platelets : 120 000/mm3
- Low HDL cholesterol

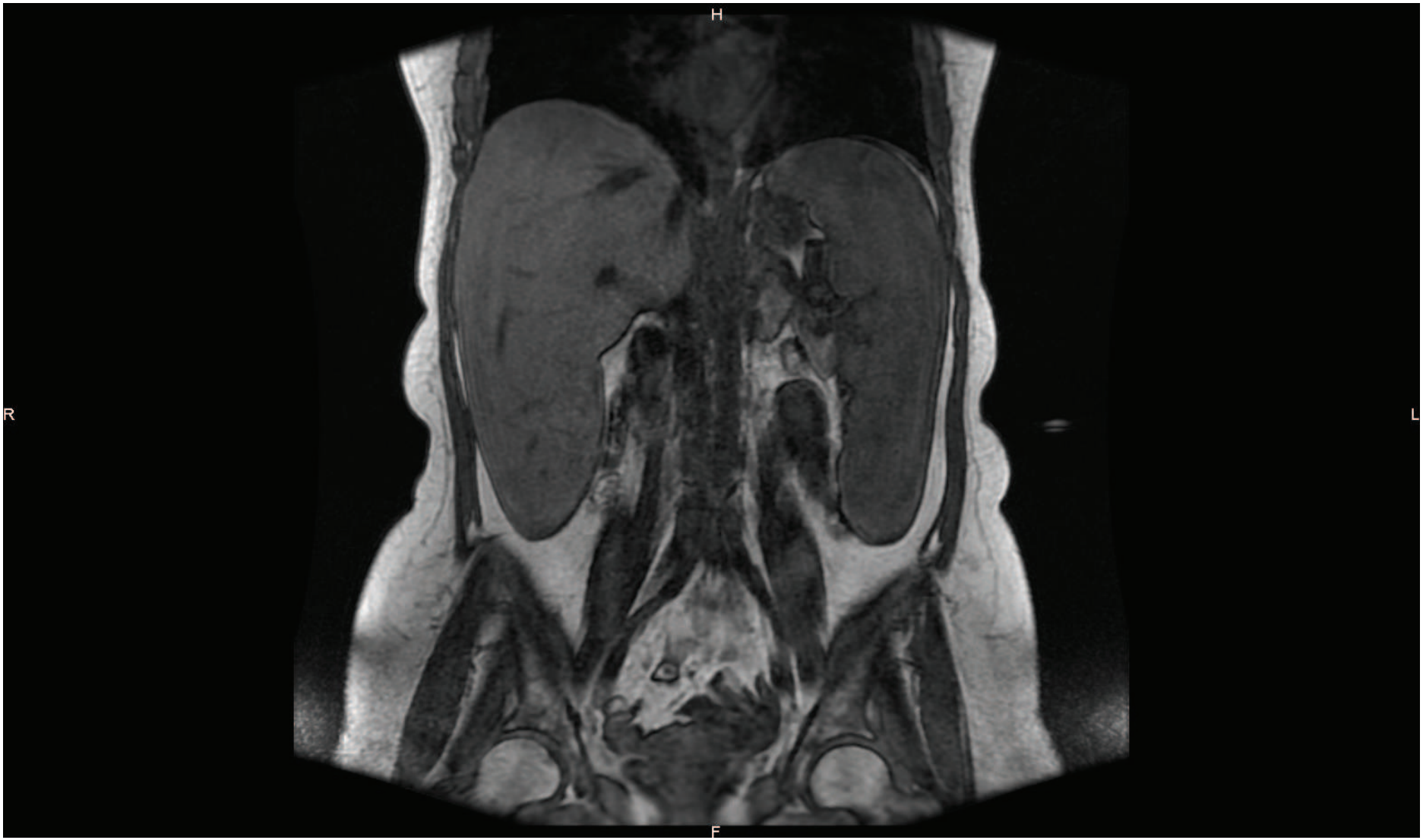
Lung involvement



Liver and spleen enlargement



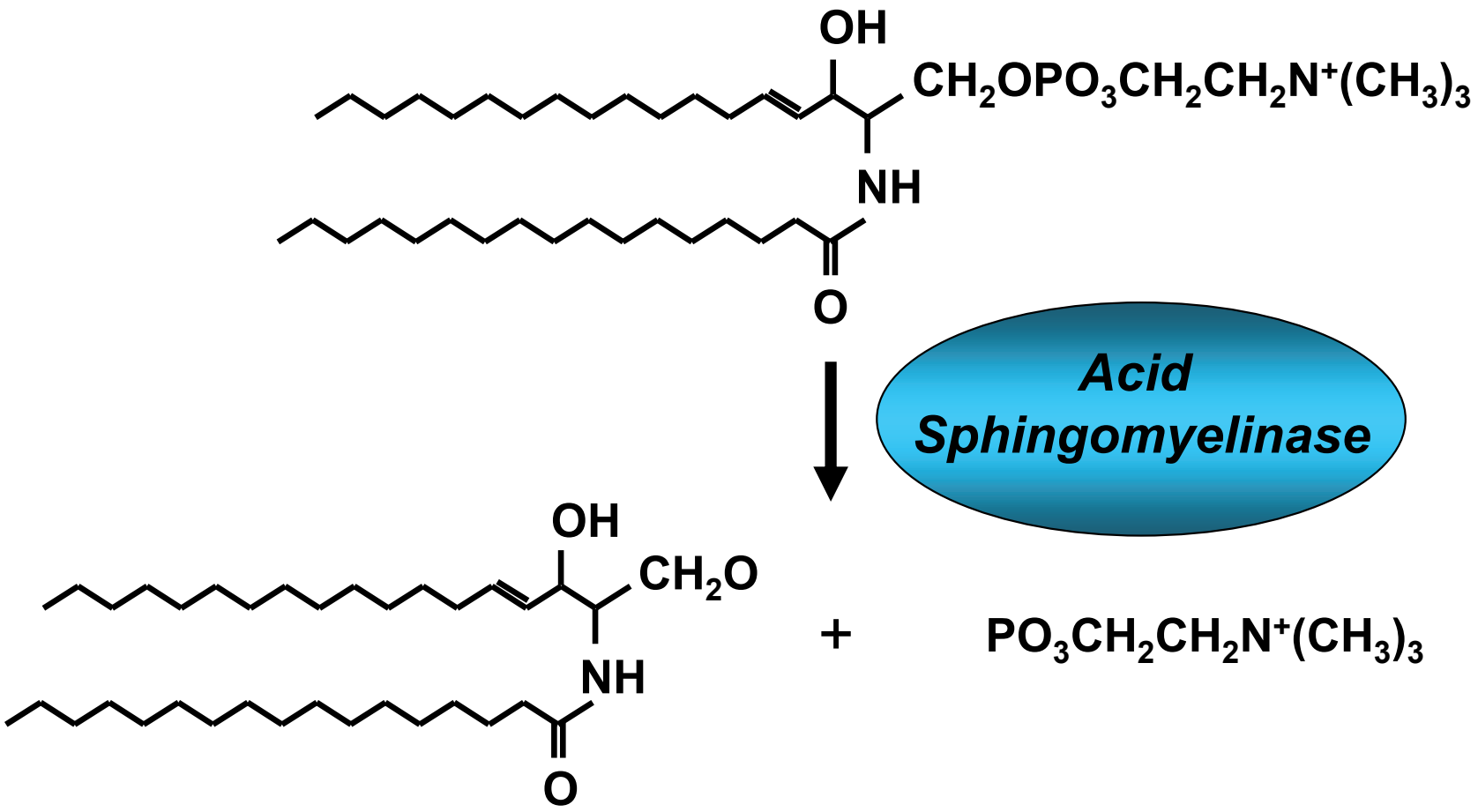
Liver and spleen enlargement



One question for the diagnosis …

Acid Sphingomyelinase (ASM)

Sphingomyelin



Ceramide

Phosphorylcholine

Déficit en Sphingomyélinase acide

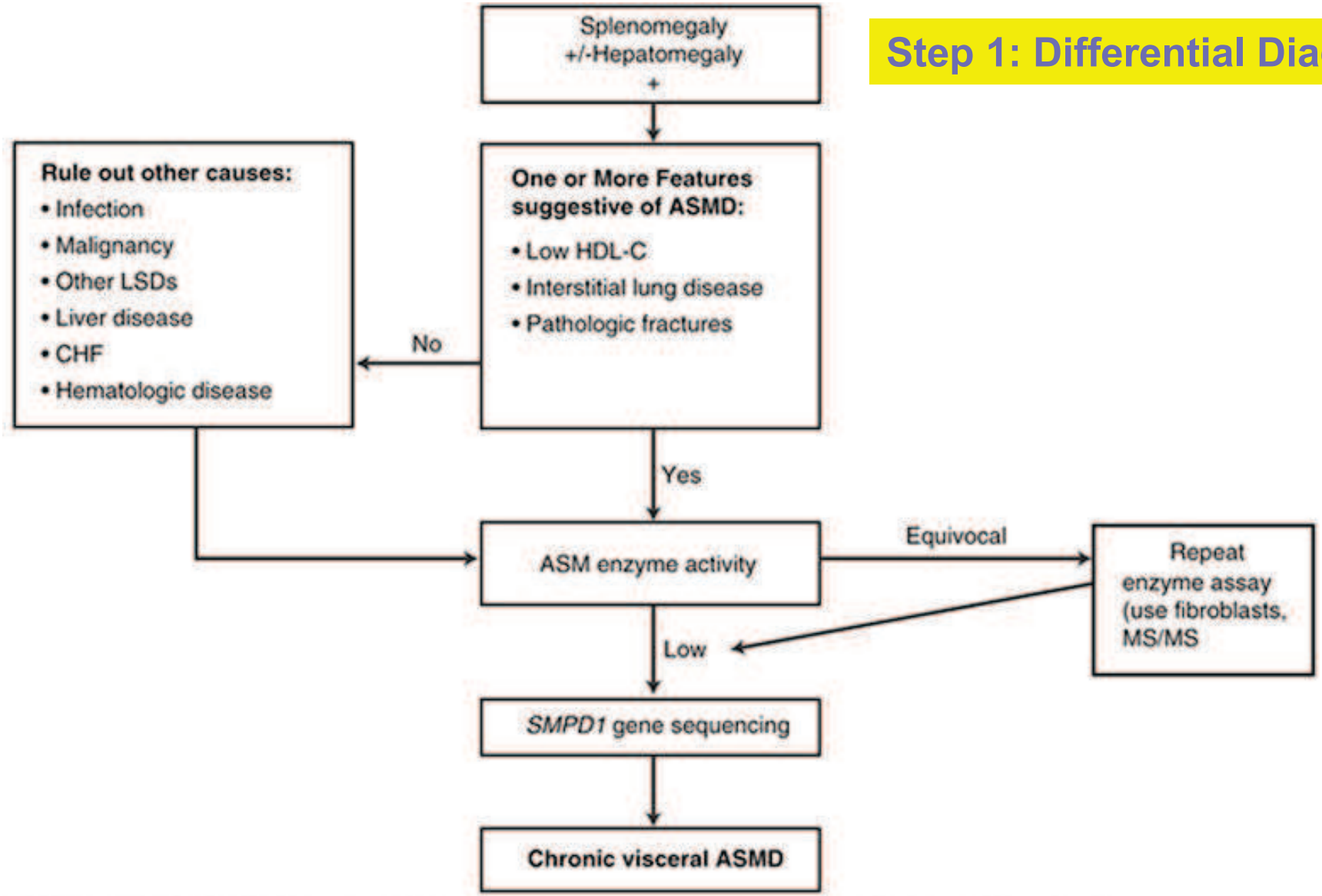
- **Niemann-Pick A et B**
- **SMPD1 = sphingomyelin phosphodiesterase 1 = acid sphigomyelinase**
  - **11p15.11p15.4**
  - **Autosomique récessif**
  - **2 allèles A : type A**
  - **2 allèles B : type B**
  - **1 A et 1 B : type B**
- **Estimation : 1/250 000**

Niemann Pick type B

- **Initial presentation**
  - **Spleen 78%**
  - **Liver 73%**
- **Symptoms**
  - **Bleeding 49%**
  - **Pulmonary infections 42%**
  - **Shortness of breath 42%**
  - **Joint/limb pain : 39%**

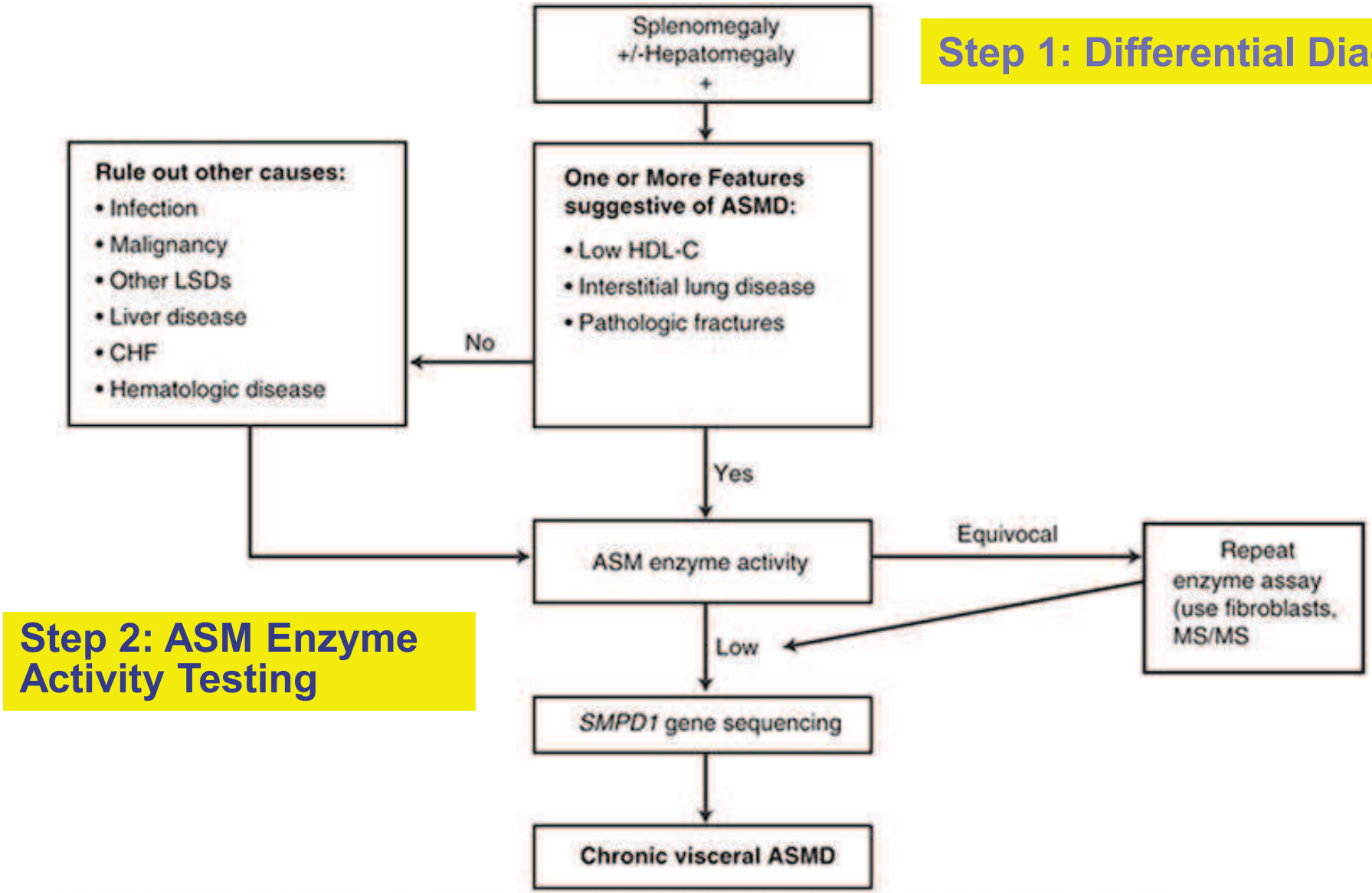
McGovern MM, et al. Paediatrics 2008.

Step 1: Differential Diagnosis



Abbreviations: ASM = acid sphingomyelinase; ASMD = acid sphingomyelinase deficiency; CHF = congestive heart failure; HDL-C = high density lipoprotein cholesterol; LSD = lysosomal storage disorder; MS/MS = tandem mass spectrometry; *SMPD1* = ASM gene

Diagnostic algorithm for acid sphingomyelinase deficiency presenting after childhood.
McGovern MM et al. Orphanet J Rare Dis 2017;12:41.



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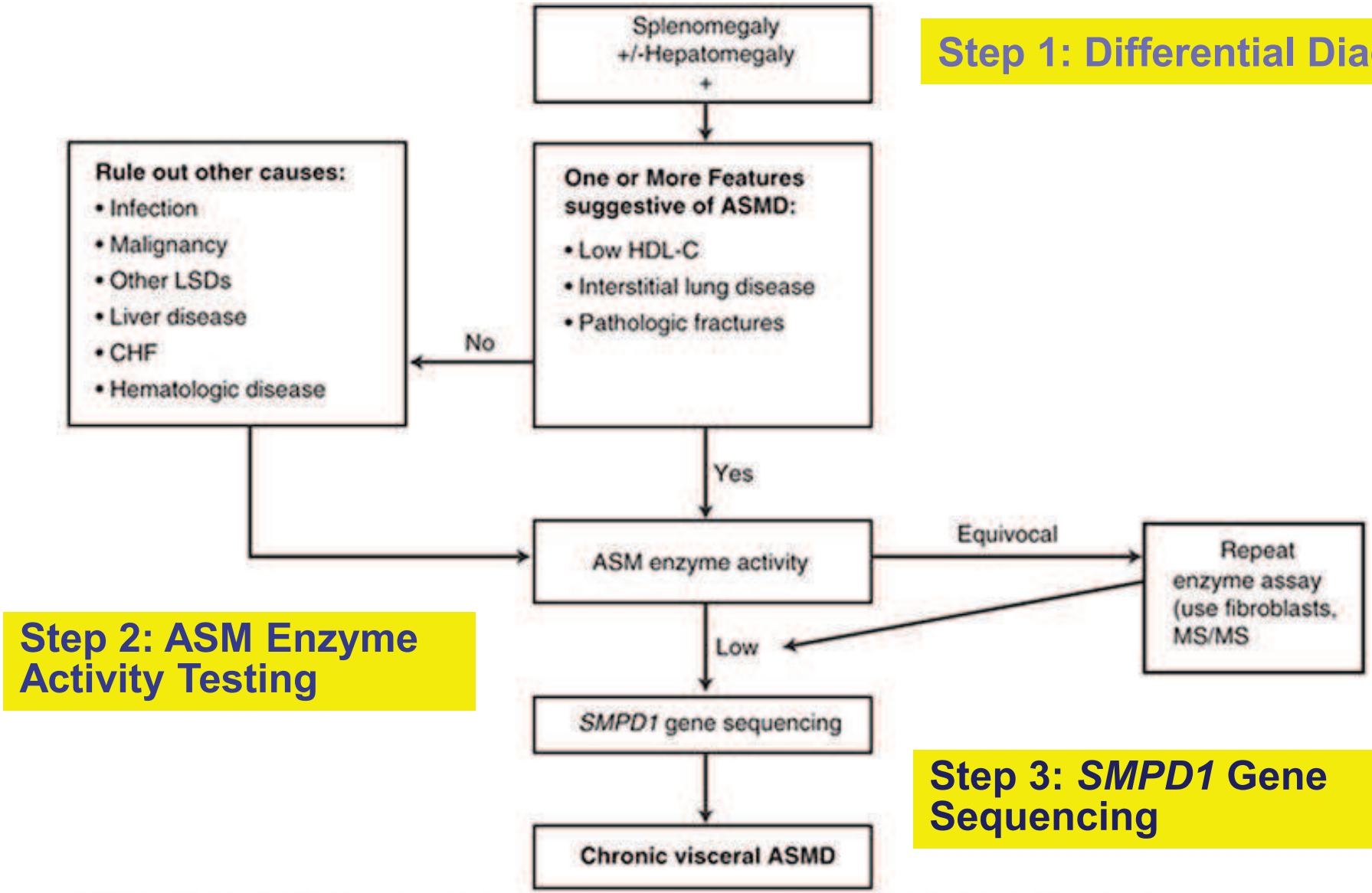

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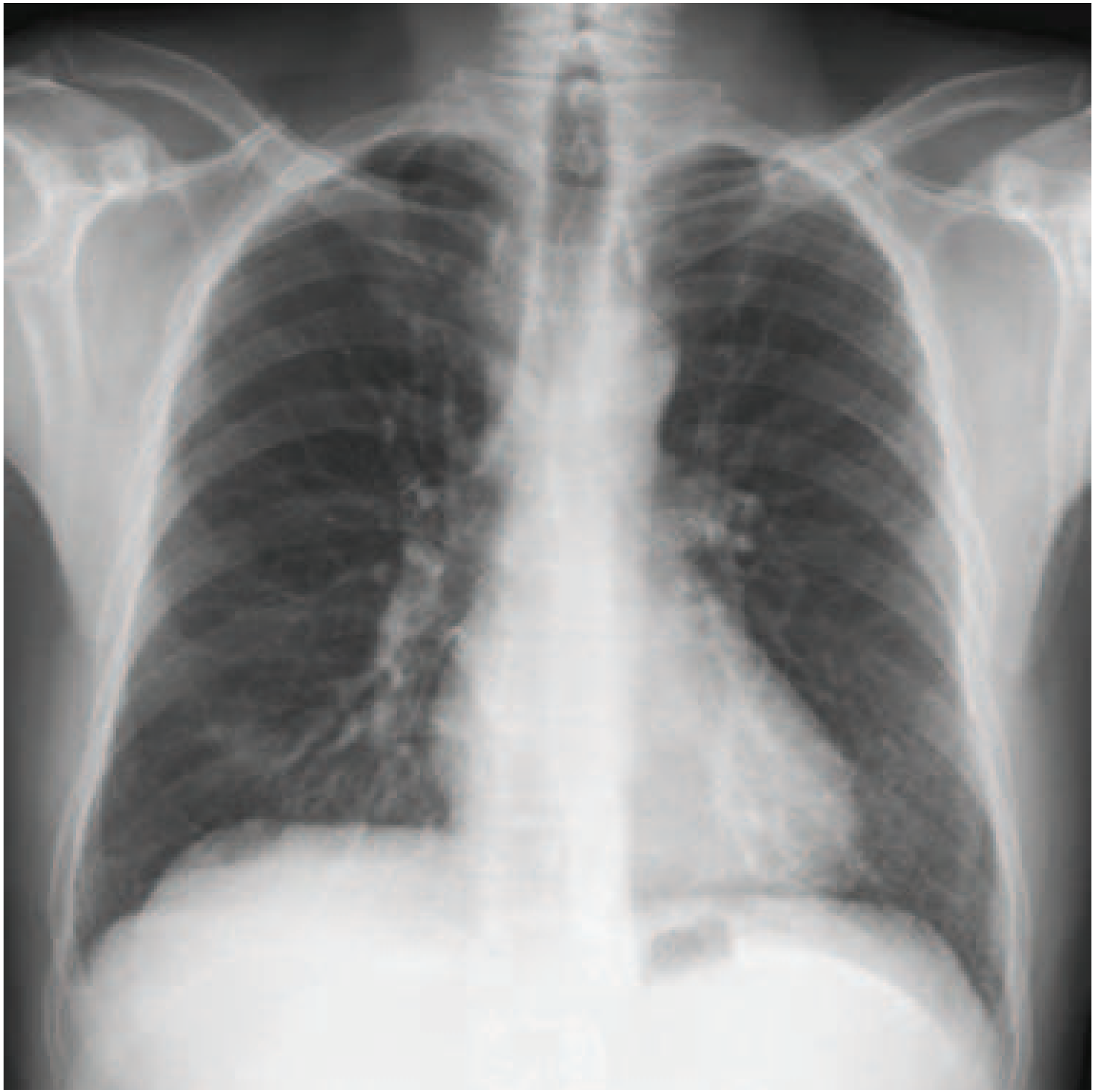
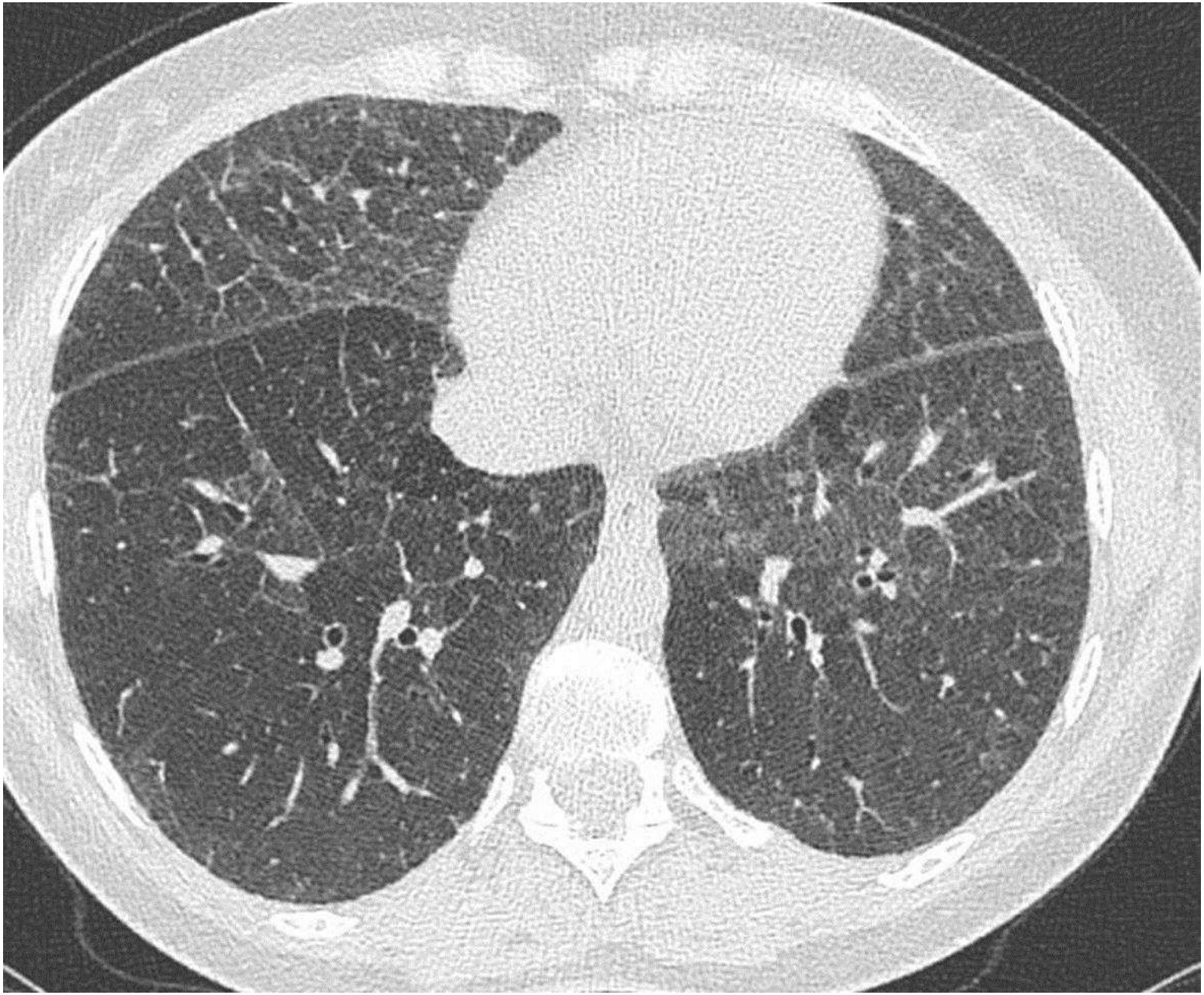
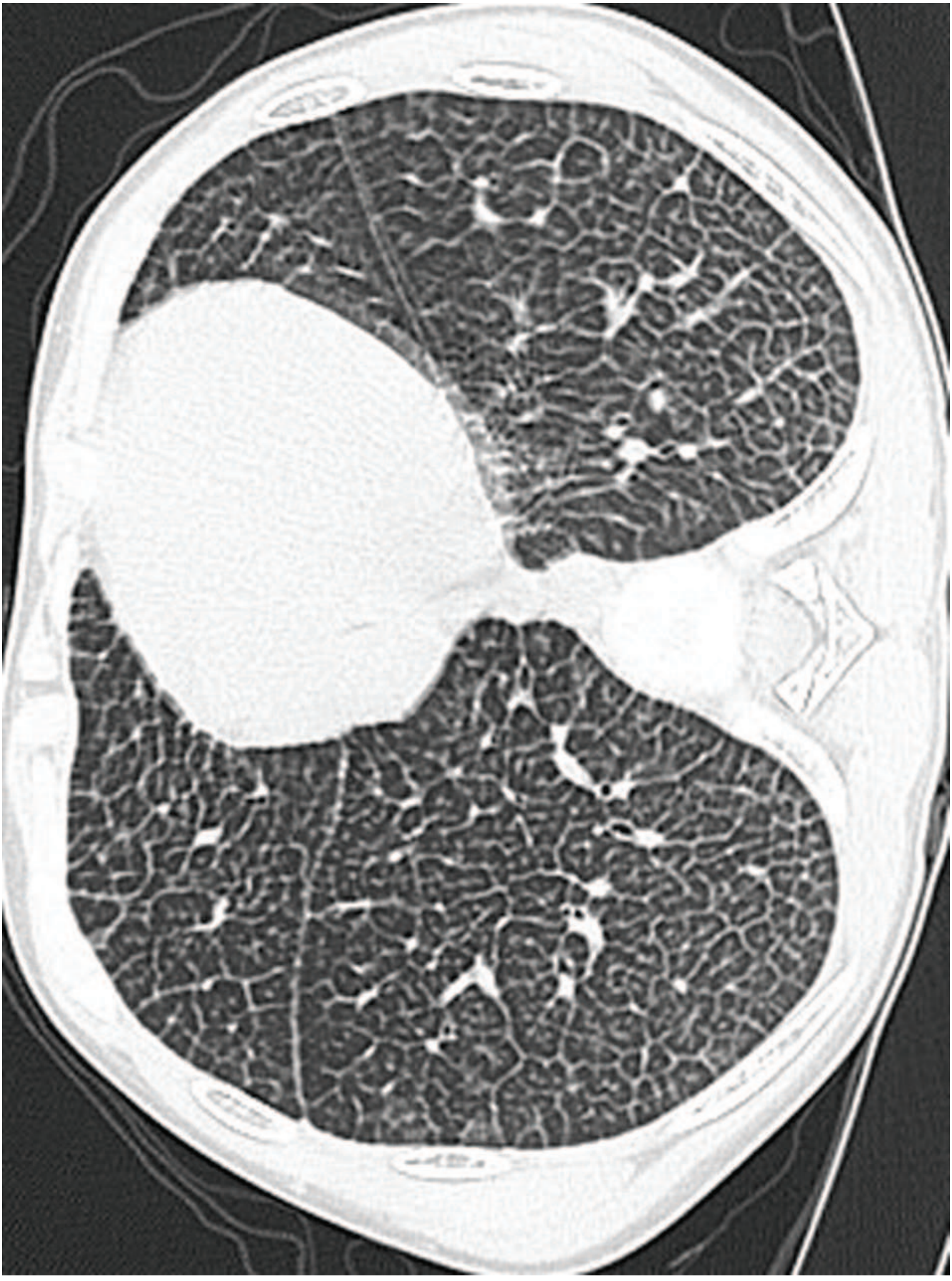
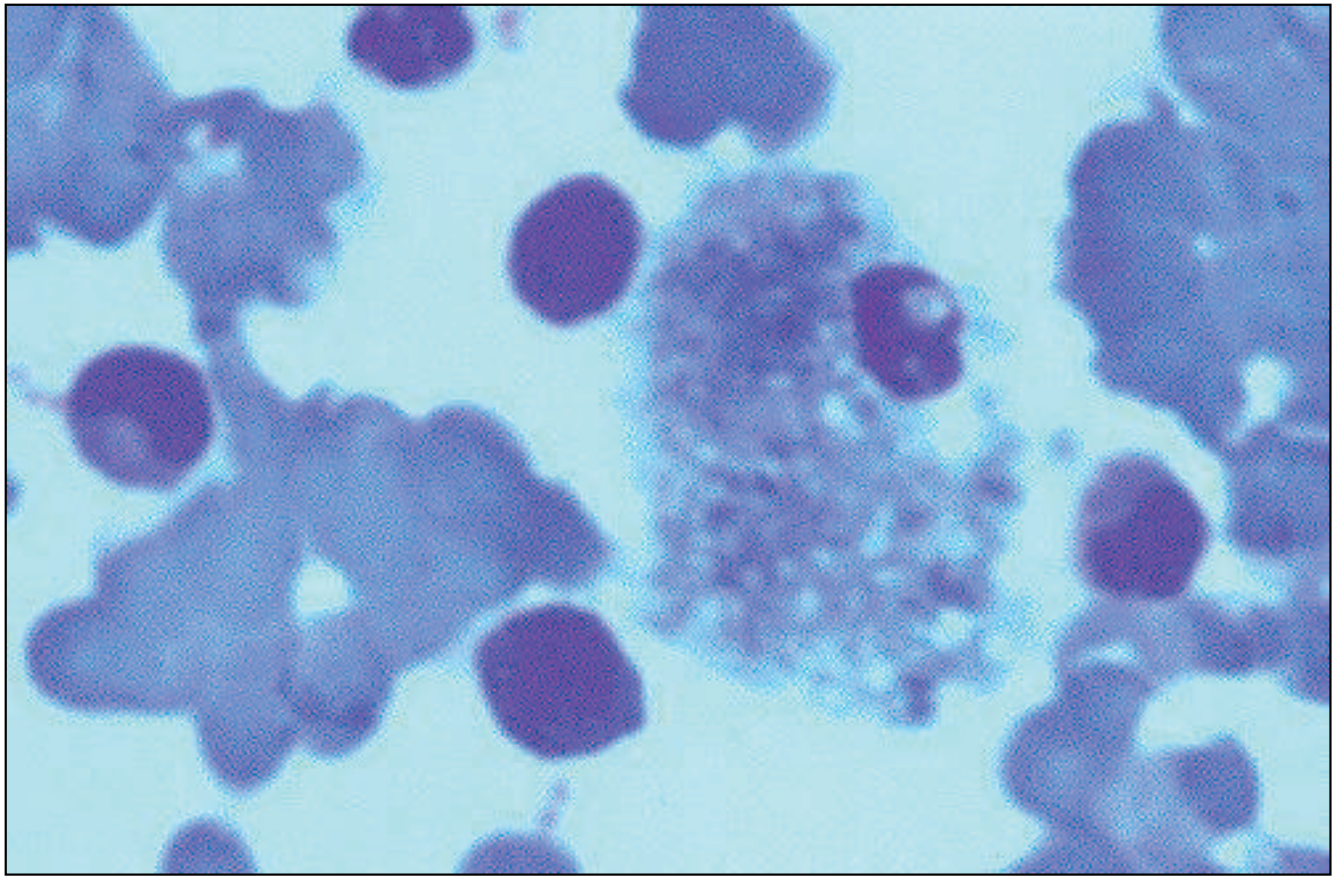




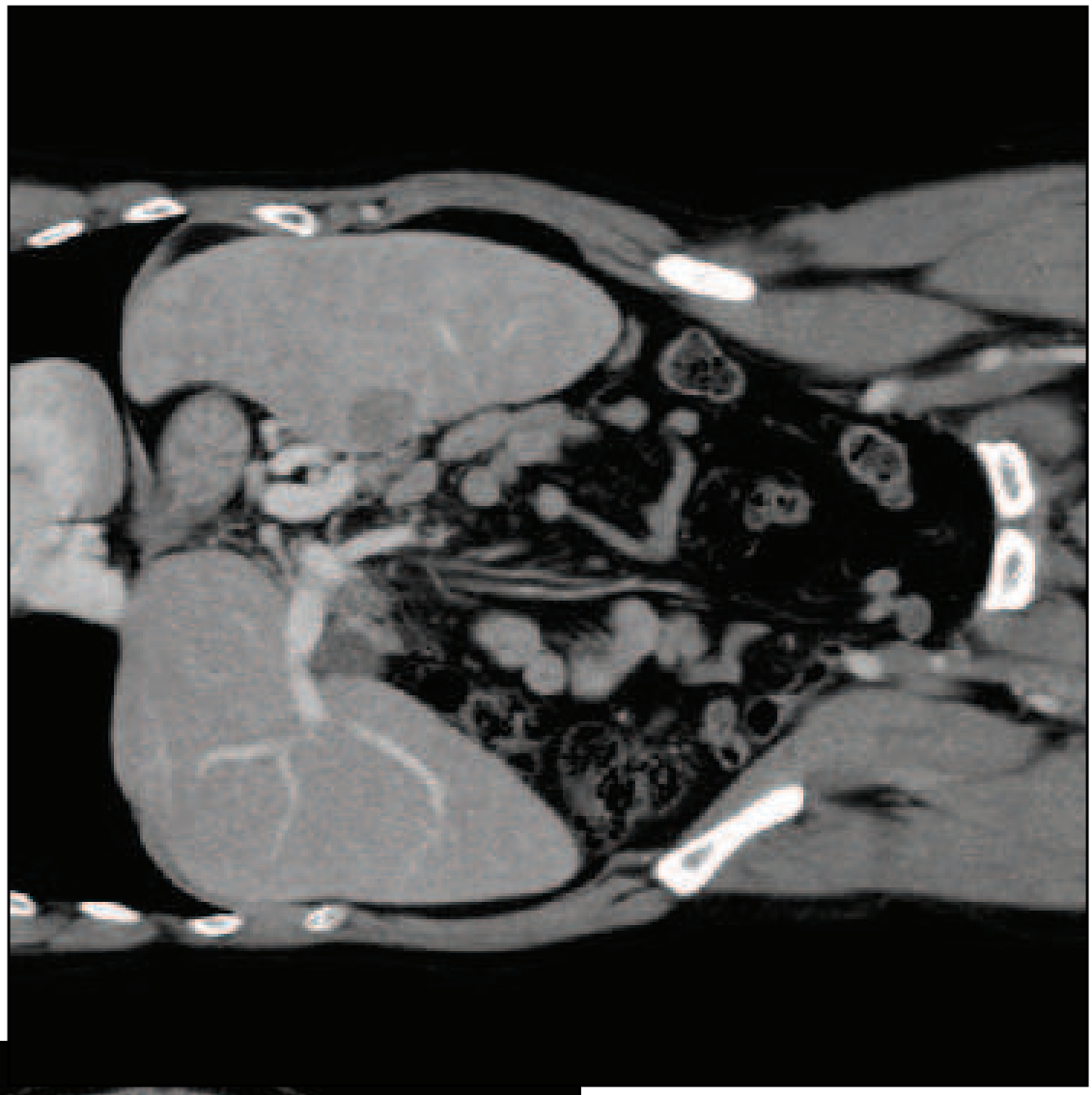
Remerciements au Pr A. Tazi, Pneumologie, Hôpital St Louis, Paris.

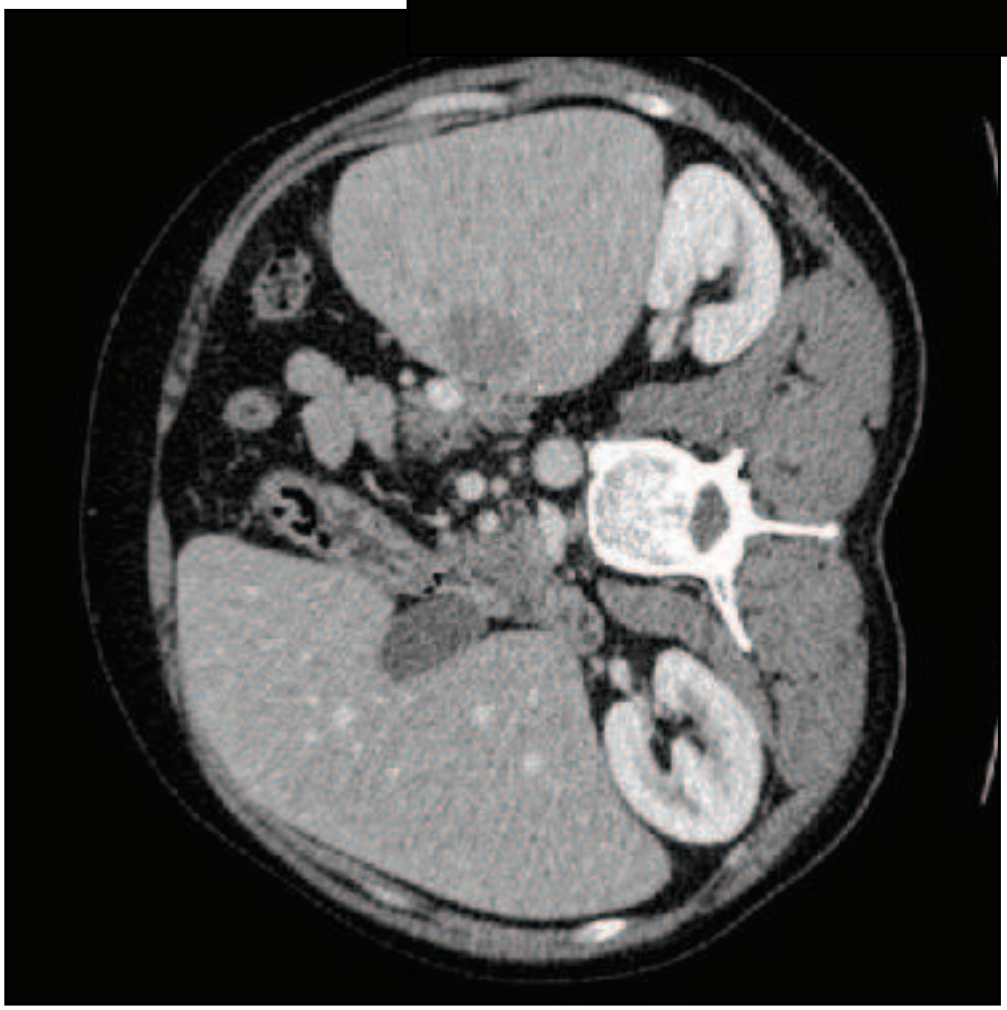


Niemann-Pick (myélogramme)

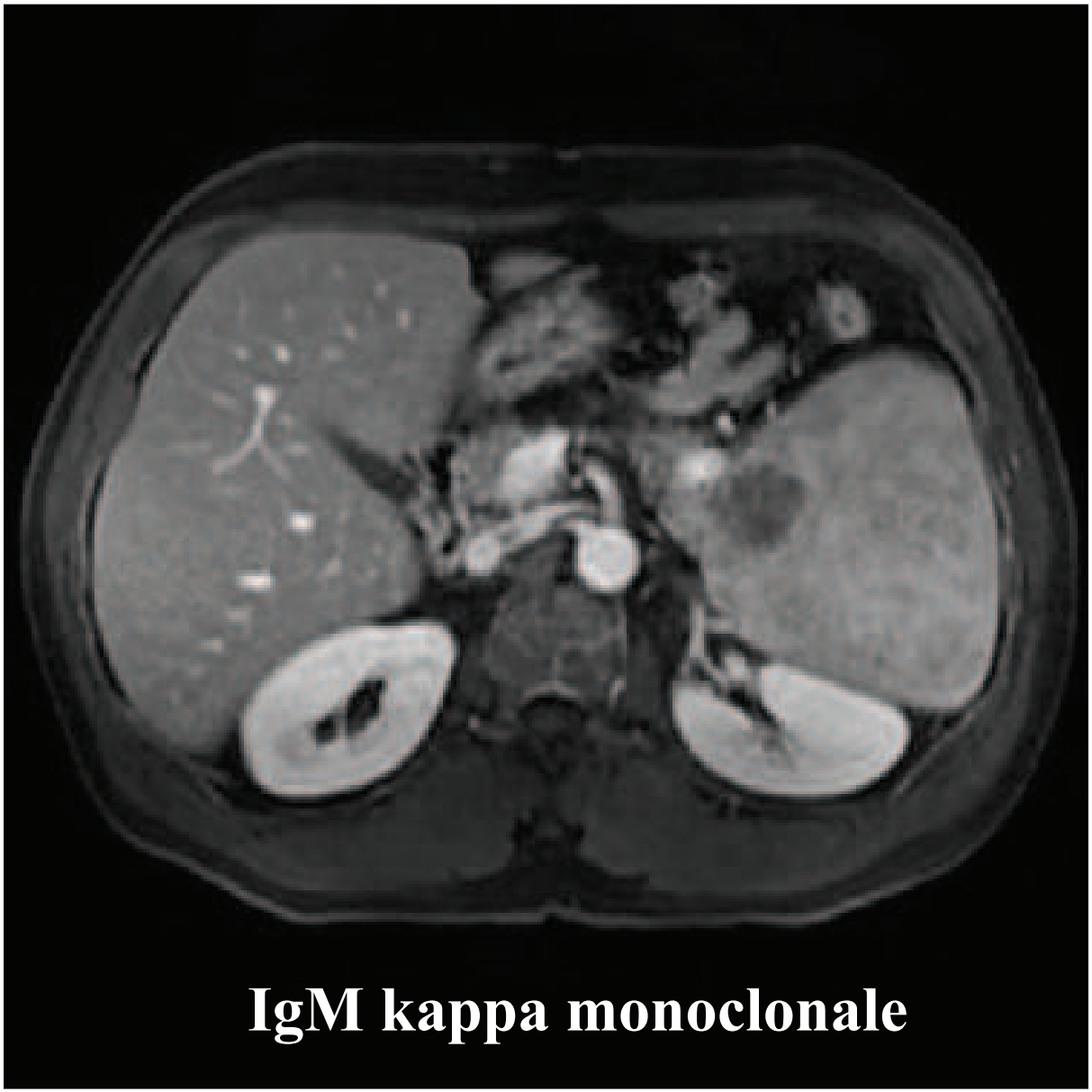


pathologyoutlines.com





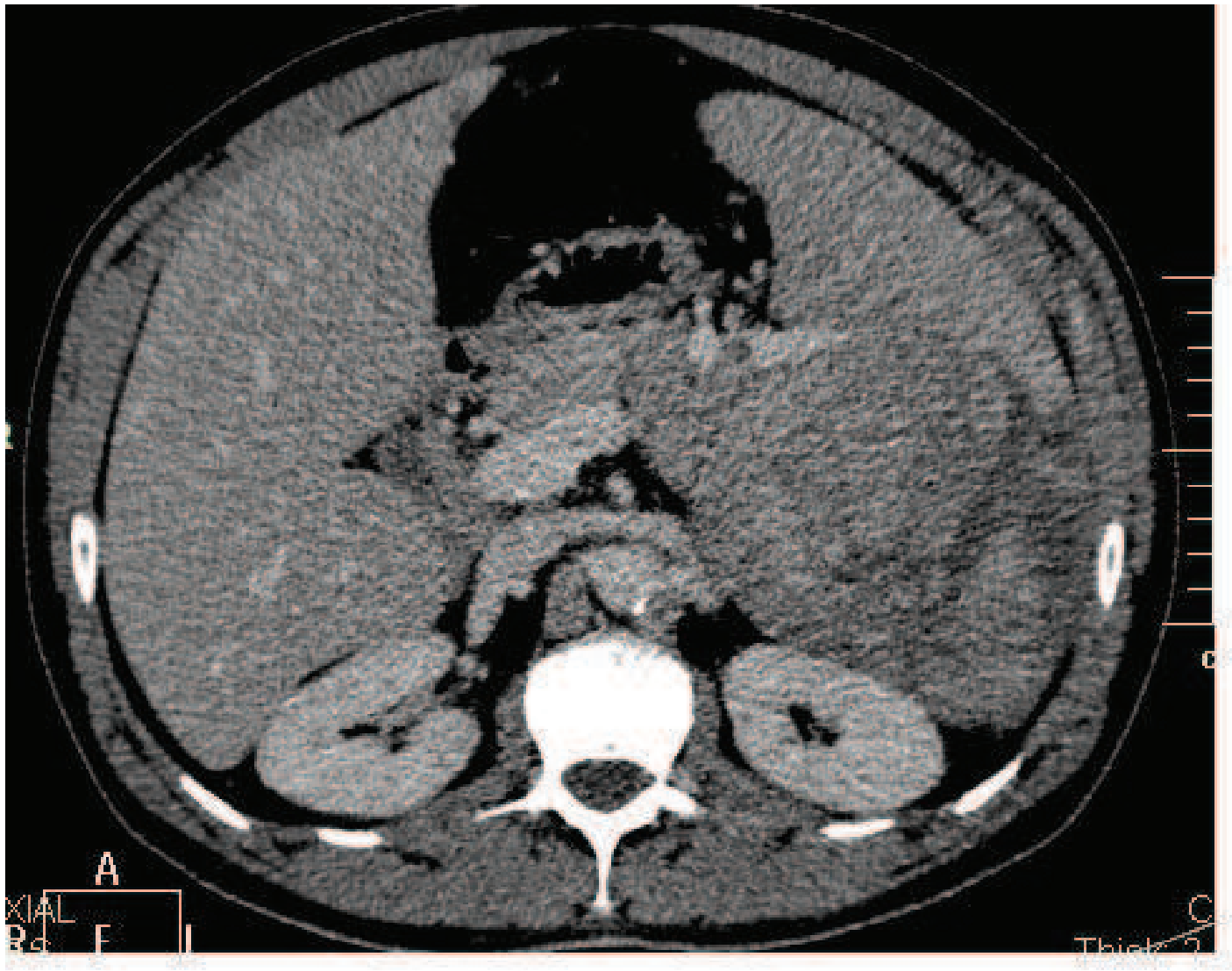
Splenectomie ?



IgM kappa monoclonale

Pas de fièvre

Pas de ganglion



Rupture splénique : quel est votre traitement ?

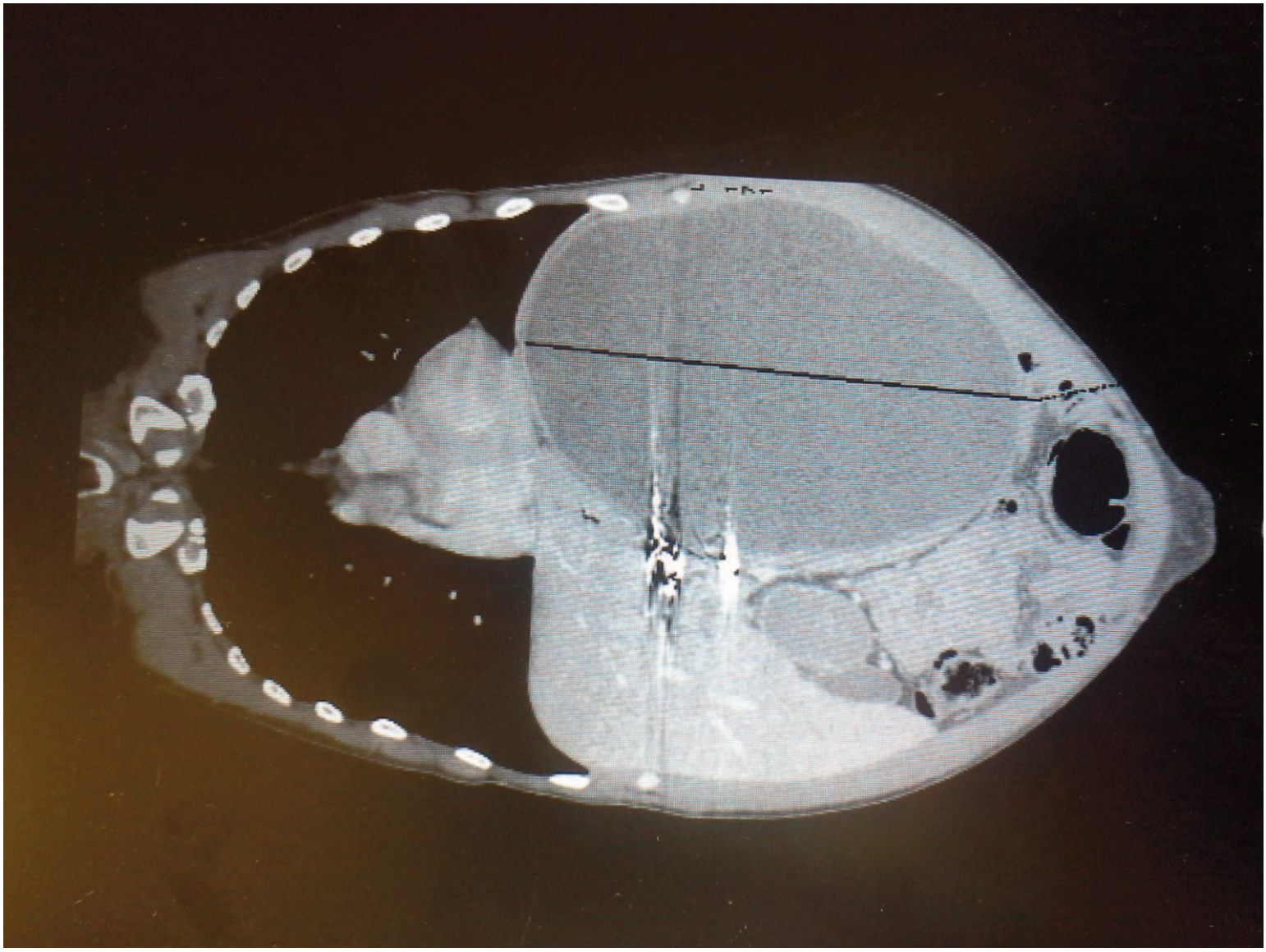
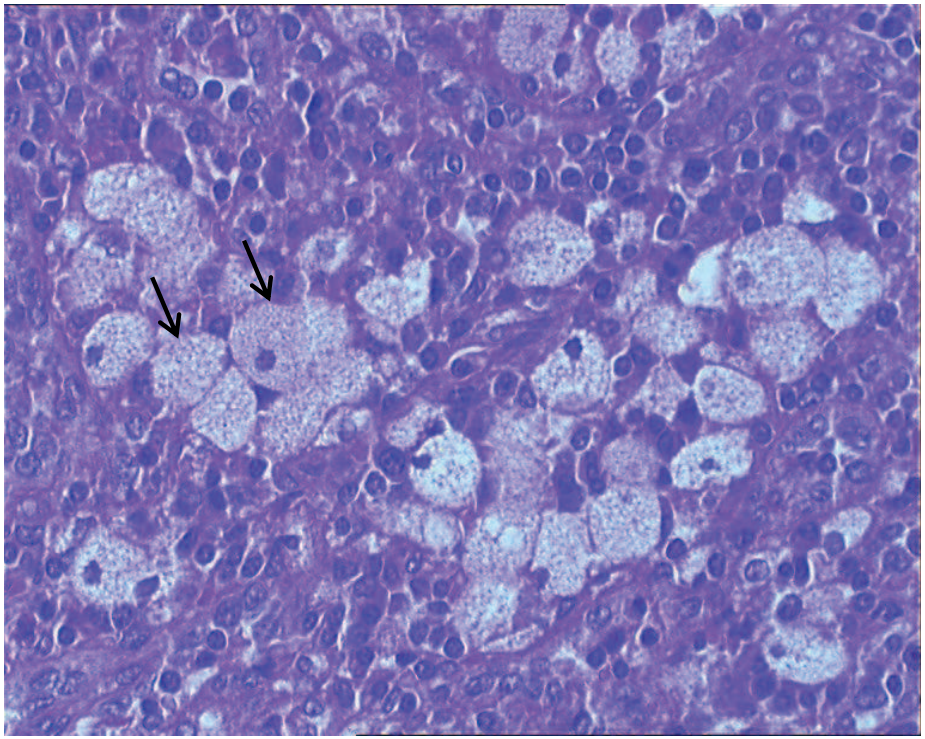


Figure 1: foamy macrophages with accumulation of lipids (HES X200)

Figure 1: amas d'histiocytes spumeux riches en lipides (HES X200)



Lidove O, Le Fèvre L, et al. Rev Med Interne 2015

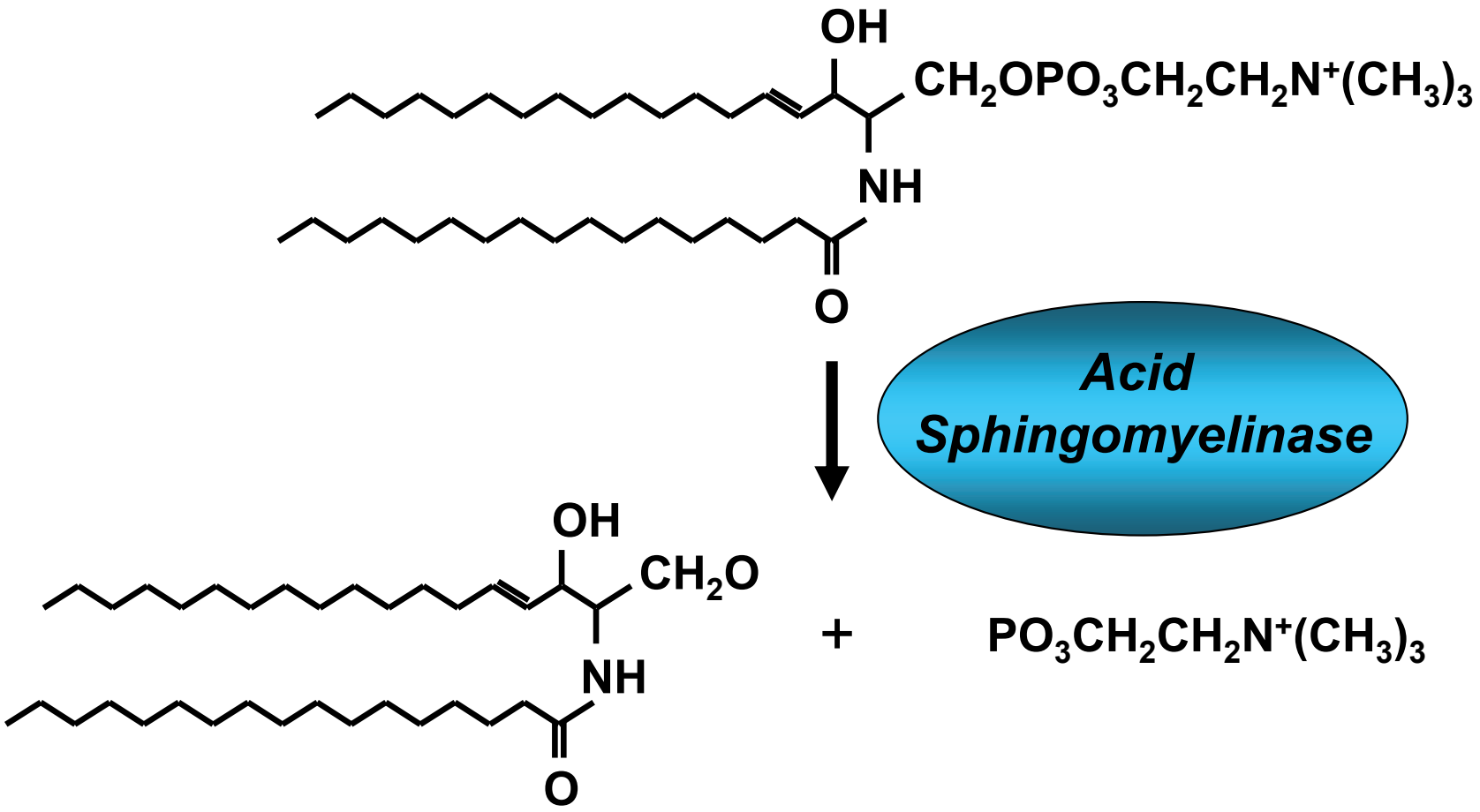
Profil lipidique

- 10 NP A, 30 NP B
- **HDLc diminué : 100%**
- TG augmentés : 25/40 (62%)
- LDLc augmenté : 27/40 (67%)

McGovern MM, et al. J Pediatr 2004.

Recombinant Human Acid Sphingomyelinase (rhASM)

Sphingomyelin



Ceramide

Phosphorylcholine

Niemann-Pick B : phase I

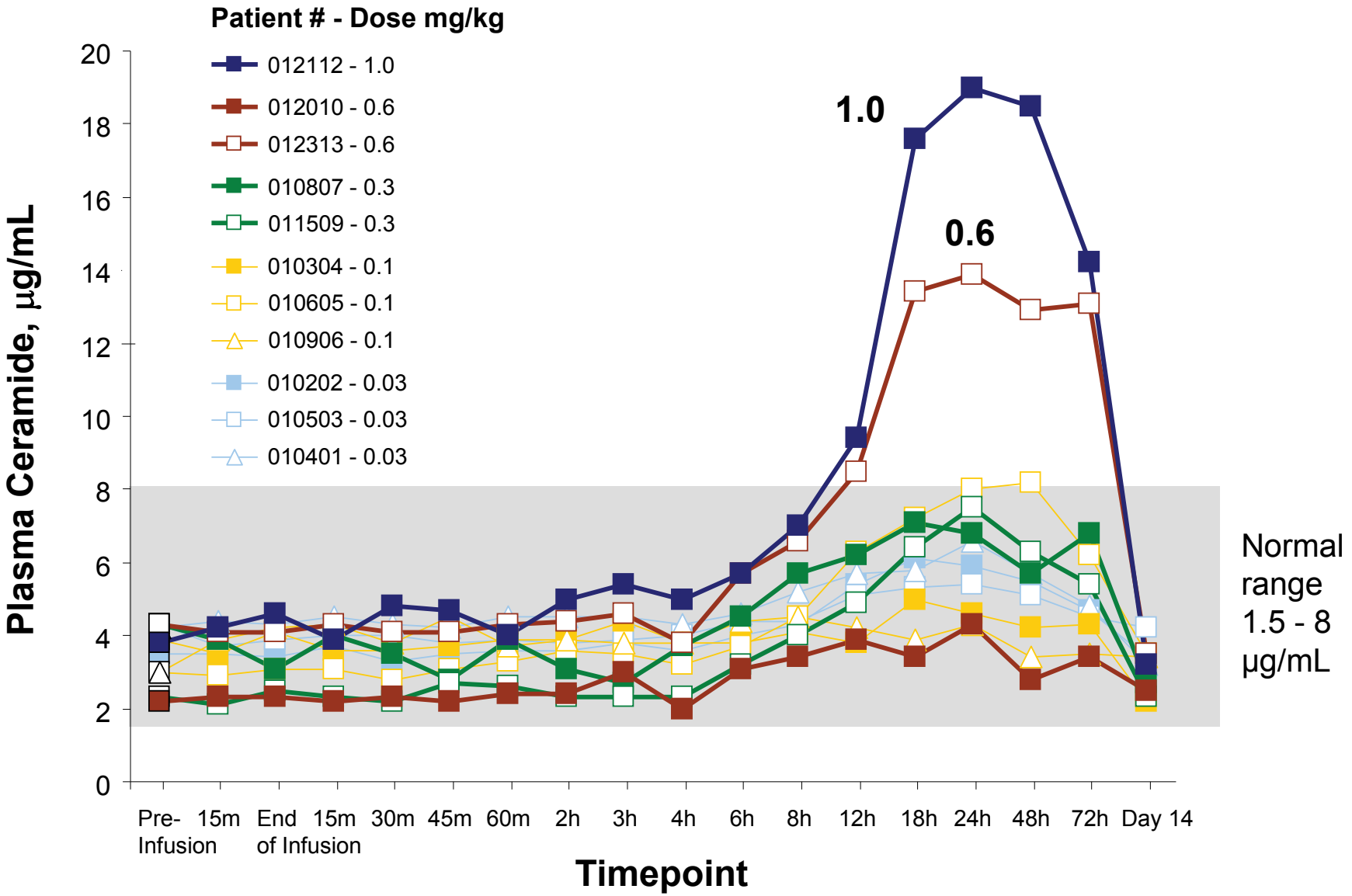
Design et objectifs : single ascending dose study to evaluate the safety and pk profile of single doses of rhASM in ASMD patients

- Janvier 2007 -> fin Mars 2009 ; 11 adultes
- 1 seul centre (Mount Sinaï Hospital, New York)
- Doses :
  - 0.03 et 0.1 mg/kg (3 patients / dose)
  - 0.3 et 0.6 mg/kg (2 patients /dose)
  - 1 mg/kg (1 patient)

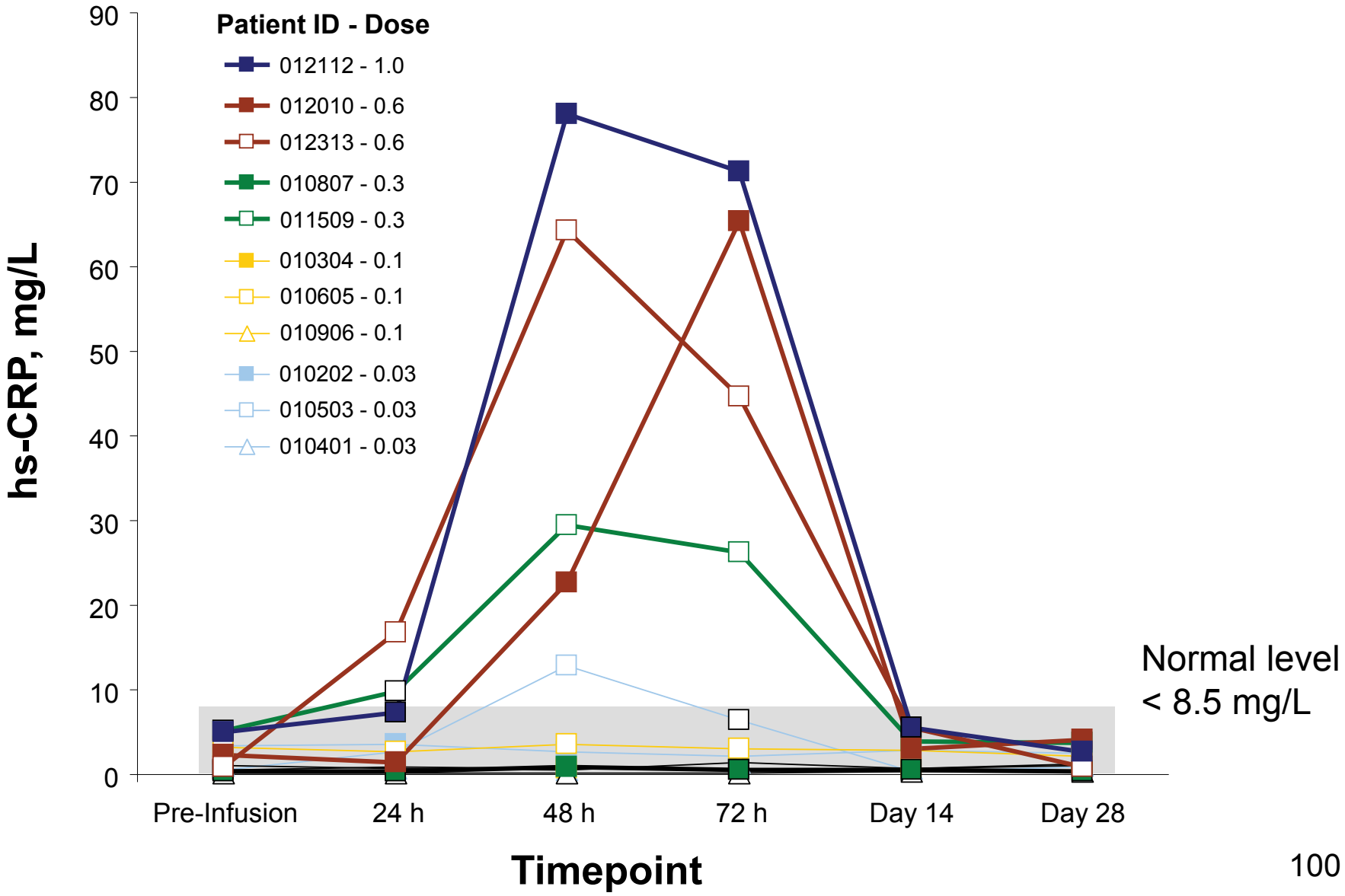
- Tolérance, pK, pD

McGovern MM, et al. Genet Med 2016;18:34-40.

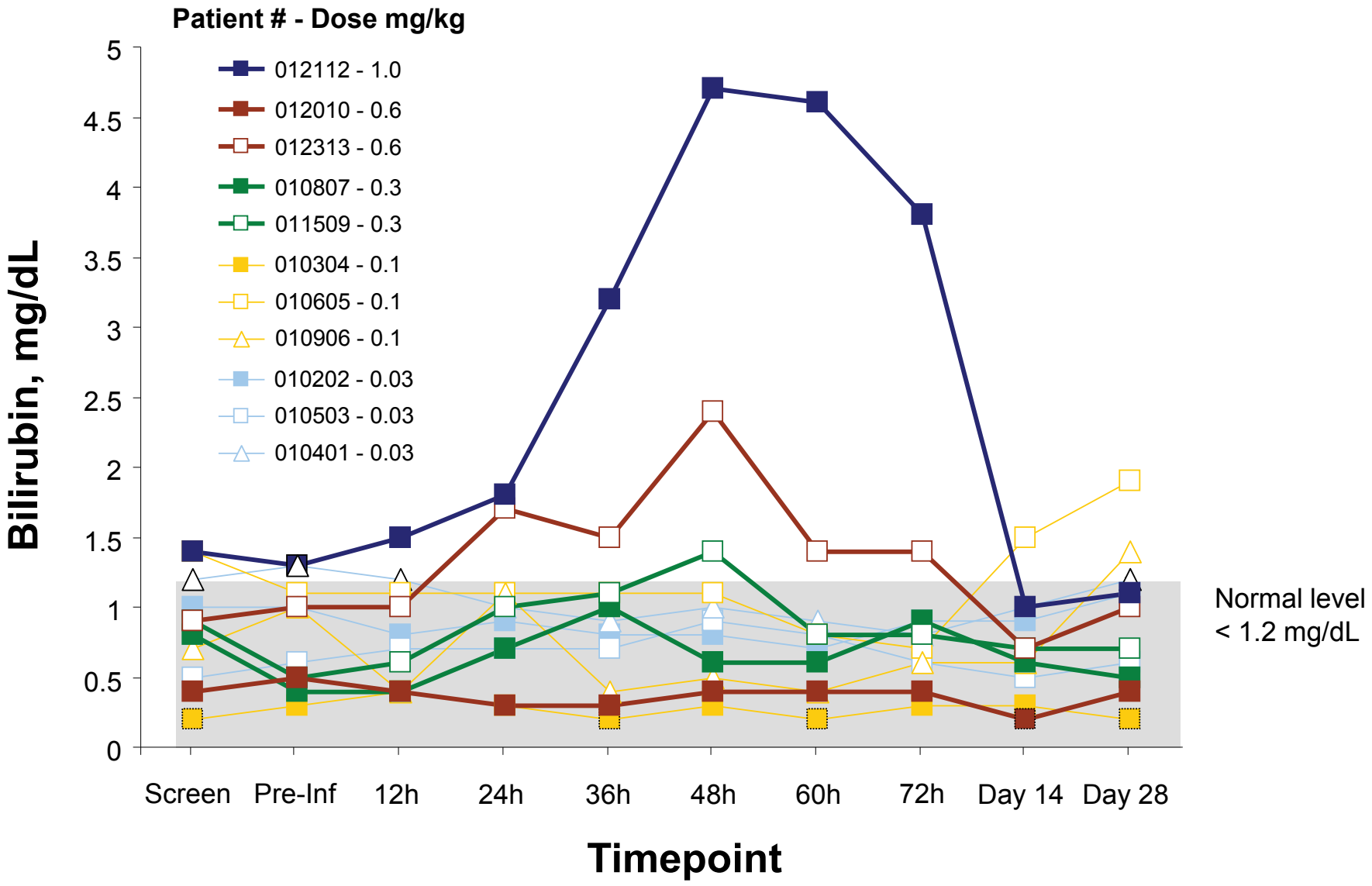
Plasma Ceramide Levels



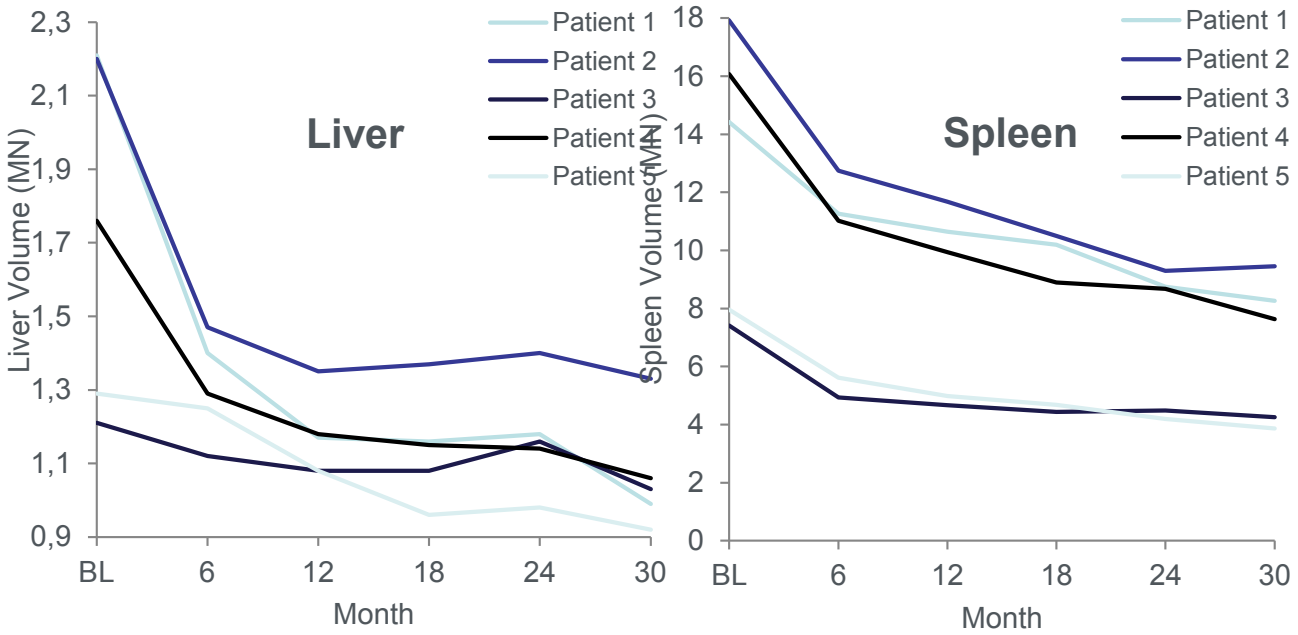
C-Reactive Protein Levels



Total Bilirubin Levels



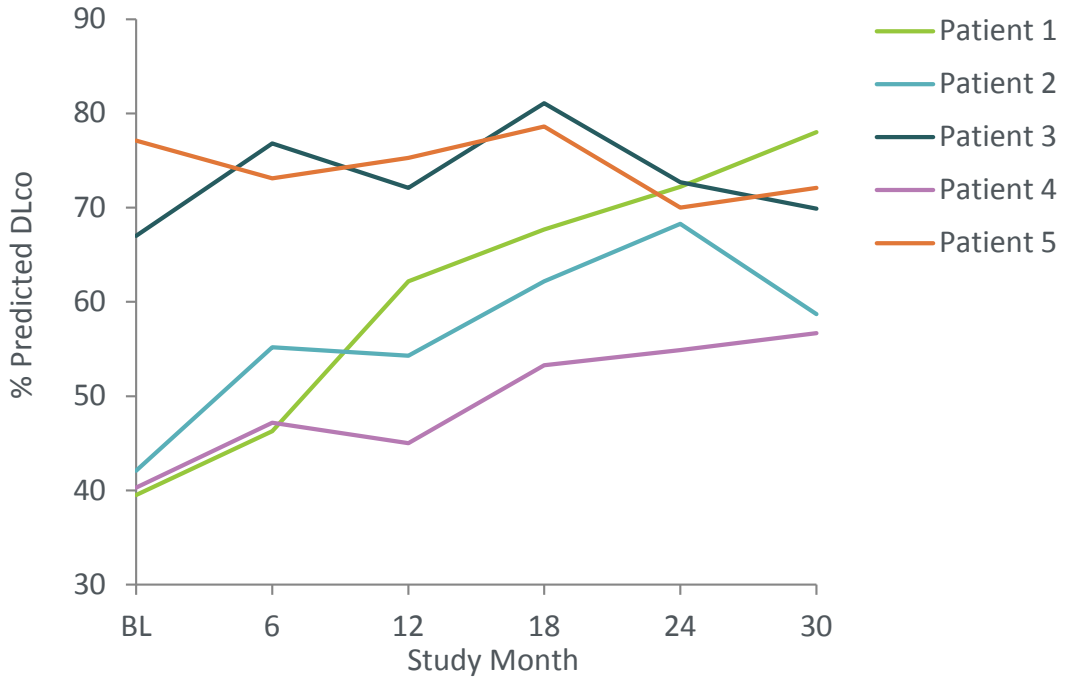
Spleen and Liver Volumes



- Spleen and liver volumes decreased in all patients relative to baseline
- Mean spleen volumes decreased from 12.8 multiples of normal (MN) at baseline to 6.7 MN at 30 months, >47% decrease from baseline ($p<0.0001$)
- Mean liver volumes decreased from 1.7 MN at baseline to 1.1 MN at 30 months, >35% decrease from baseline ($p=0.006$)

Wasserstein 2018. Journal of Inherited Metabolic Disease https://doi.org/10.1007/s10545-017-0123-6

Infiltrative Lung Disease – % Predicted DL_{CO}



- Mean percent predicted DL_{CO} increased from 53.2% predicted at baseline to 67.08% predicted (mildly reduced DL_{CO}) at 30 months
- The most prominent changes were observed in the 3 patients with the lower DL_{CO} values at baseline

Wasserstein 2018. Journal of Inherited Metabolic Disease
https://doi.org/10.1007/s10545-017-0123-6

Conclusion

- **Maladie de Niemann Pick B (autosomique récessive):**
  - Hépato-splénomégalie
  - Fibrose interstitielle pulmonaire (crépitants antérieurs)
  - Risque hémoragique (thrombopénie)
  - Profil lipidique athérogène (HDLc effondré)
- **Médecins concernés :**
  - Pédiatres
  - Pneumologues, hépatologues, hématologues, …

- **Traitement par enzymothérapie recombinante (essai thérapeutique de phase 2/3 en cours)**

Synthèse

Niemann Pick B vs Fabry (1)

Niemann Pick B	Fabry
• Maladie lysosomale	• Maladie lysosomale
• Accumulation de substrat	• Accumulation de substrat
• Hommes et femmes	• **Hommes** et femmes
• Fibrose	• Ischémie - Fibrose

Niemann Pick B vs Fabry (2)

Niemann Pick B

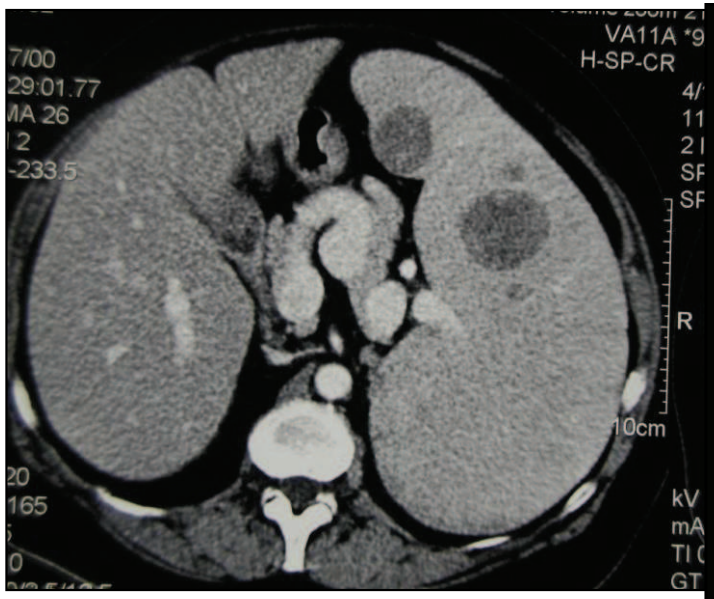
- AR (consanguinité)
- Macrophage
- Phénotype « serré »
- Phase 2/3 …
  - Céramide pro-inflammatoire

Fabry

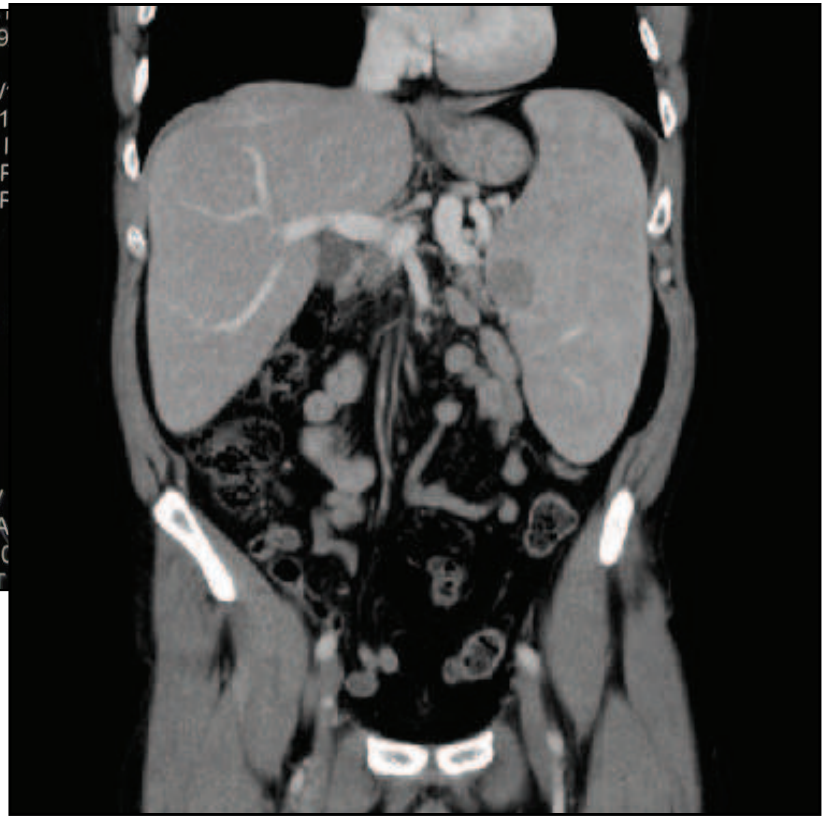
- Liée à l'X (famille)
- Cellule endothéliale
- Phénotype polymorphe
- Enzymothérapies
  - Ac anti-enzymes
  - Point de non-retour = fibrose

Tableaux cliniques

- **Macrophage**

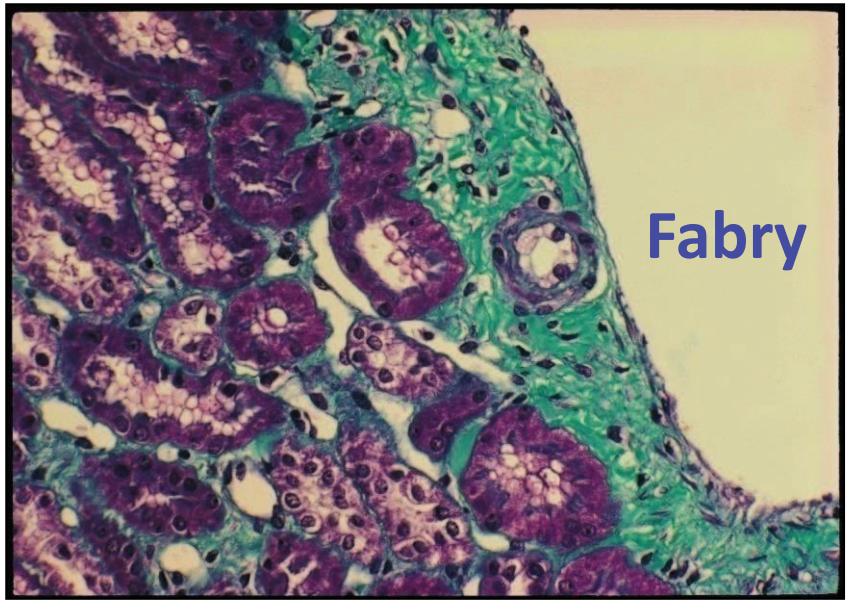


Gaucher type 1



Niemann-Pick type B

- **Cellule endothéliale**



Remerciements

- **Patients et familles**
- **Associations de patients :**
  - **APMF**
  - **VML**
- **CRML**
- **Co-auteurs des travaux**
  - Groupe collaboratif français
- **Collaborateurs**
  - **Cliniciens**
  - **Biochimistes**
  - **Généticiens**

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Association des Patients de la Maladie de Fabry

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