SoFFœt
Société Française de Fœtopathologie

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PHENOTYPE HEMOCHROMATOSE NEONATALE
FOIE ET SURCHARGE EN FER FŒTALE ET PERINATALE: QUELS DIAGNOSTICS ?

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Hémochromatose néonatale
Définition et problématiques

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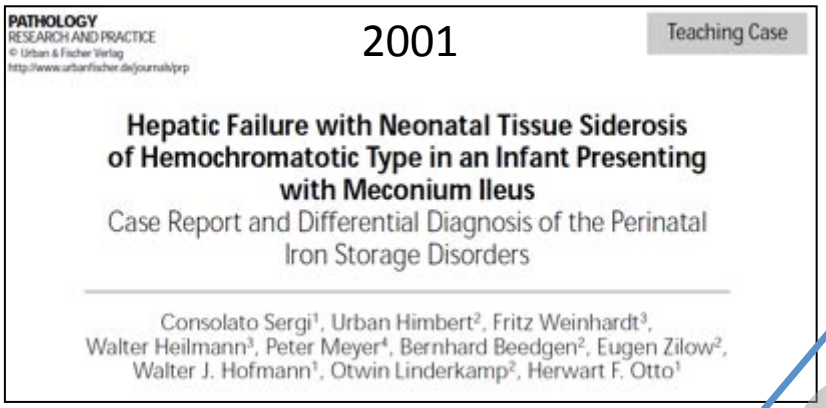
NH: definition

- rare disease
- fetus and neonate
- H Cottier 1957
- hepatic and extrahepatic siderosis sparing the reticuloendothelial system
- and severe liver disease

NH is a phenotype : several etiologies



PATHOLOGY
RESEARCH AND PRACTICE
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2001

Teaching Case

Hepatic Failure with Neonatal Tissue Siderosis of Hemochromatotic Type in an Infant Presenting with Meconium Ileus

Case Report and Differential Diagnosis of the Perinatal Iron Storage Disorders

Consolato Sergi[1], Urban Himbert[2], Fritz Weinhardt[3], Walter Heilmann[3], Peter Meyer[4], Bernhard Beedgen[2], Eugen Zilow[2], Walter J. Hofmann[1], Otwin Linderkamp[2], Herwart F. Otto[1]

2004
Peter Whitington's group
Chicago's Northwestern University
An alloimmune-mediated mechanism

Table 2. Neonatal disorders associated with iron accumulation

1. Primary neonatal iron accumulation
Familial type (autosomal recessive inheritance) [a]
Sporadic type

2. Secondary neonatal iron accumulation

2.1. Syndromic
Edward syndrome (Trisomy 18) [b]
Down syndrome (Trisomy 21, OMIM 190685) [c]
Zellweger syndrome (Cerebro-hepato-renal syndrome, OMIM 214100) [d]
Tricho-hepato-enteric syndrome (Trichorrhexis blastysis, OMIM 222470) [e]
Donohue syndrome (Leprechaunism, OMIM 246200) [f]
Renal tubular dysgenesis syndrome (OMIM 267430) [g]

2.2. Non Syndromic
Intrauterine infection [h]
Exposure to toxic agents (e.g. pyrrolizidine) [i]
Δ^4-3-oxosteroid 5β-reductase deficiency [j]
Hereditary tyrosinemia (OMIM 276700) [k]
Hemolytic disease (positive Coombs reaction) [l]
Exogeneous iron overload [m]
Congenital heart disease [n]
Neonatal lupus erythematosus syndrome [o]
Bowel obstruction [p]

Alloimmune NH

Whitington PF, Malladi P. Neonatal hemochromatosis: is it an alloimmune disease? J Pediatr Gastroenterol Nutr 2005;40:544–49.

Hypothesis based on:

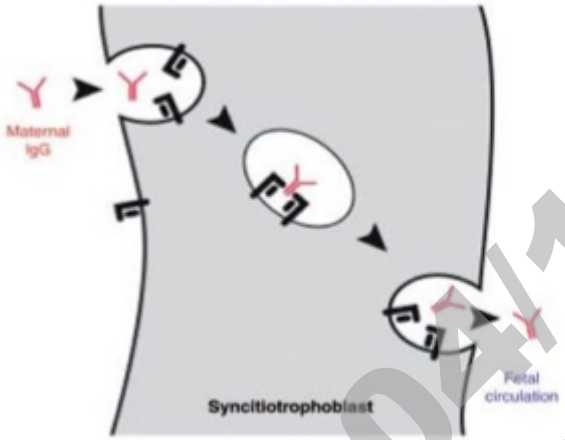
- recurrence rate > 80%
  - similar to rhesus incompatibility
  - too high for an inheritance explanation
- no mutations in genes of hereditary haemochromatosis
- affects maternal half-siblings but not paternal half-siblings
- intravenous immunoglobulin (IV-Ig) therapy
  - during pregnancy reduces the severity and the recurrence rate of the disease

    High-dose immunoglobulin during pregnancy for recurrent neonatal haemochromatosis. Whitington PF, Hibbard JU. Lancet 2004;364:1690–98.
  - in neonates: improvements in outcome

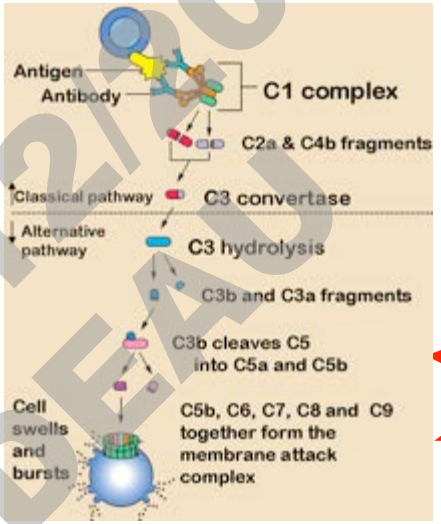
    Treatment of neonatal hemochromatosis with exchange transfusion and intravenous immunoglobulin. Rand EB, Karpen SJ, Kelly S, et al. J Pediatr 2009;155:566–71.

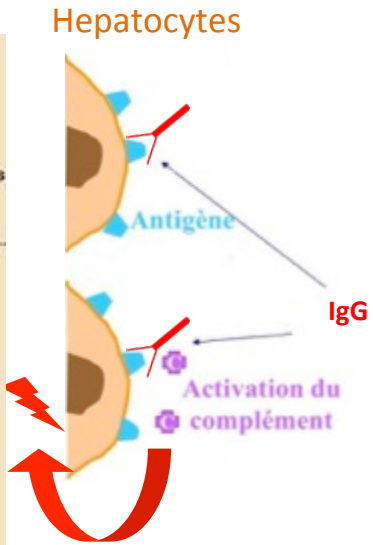
Alloimmune NH mechanisms

- maternal sensitization to a fetal hepatocyte antigen?
- Production of maternal IgG antibodies directed against this Ag



transplacental passage of the IgG antibodies occur in the subsequent pregnancy





- activation of fetal complement via the classic pathway
- formation of membrane attack complex on hepatocytes (MAC or TCC or C5b9)
- Hepatocyte injury and death

nature of the fetal hepatocyte antigen is currently still unknown

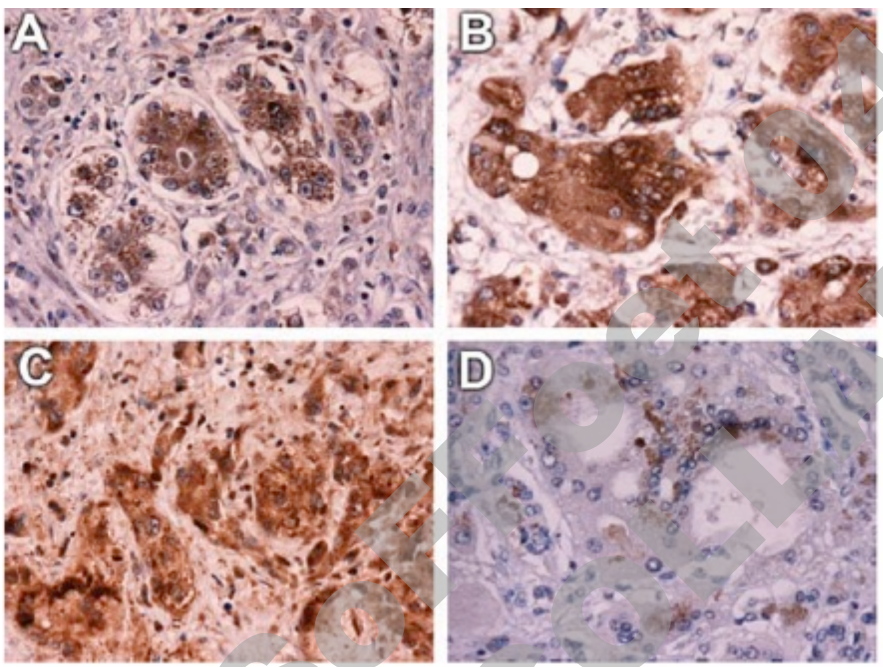
fetal complement is produced by the fetus ~12 WG

GALD

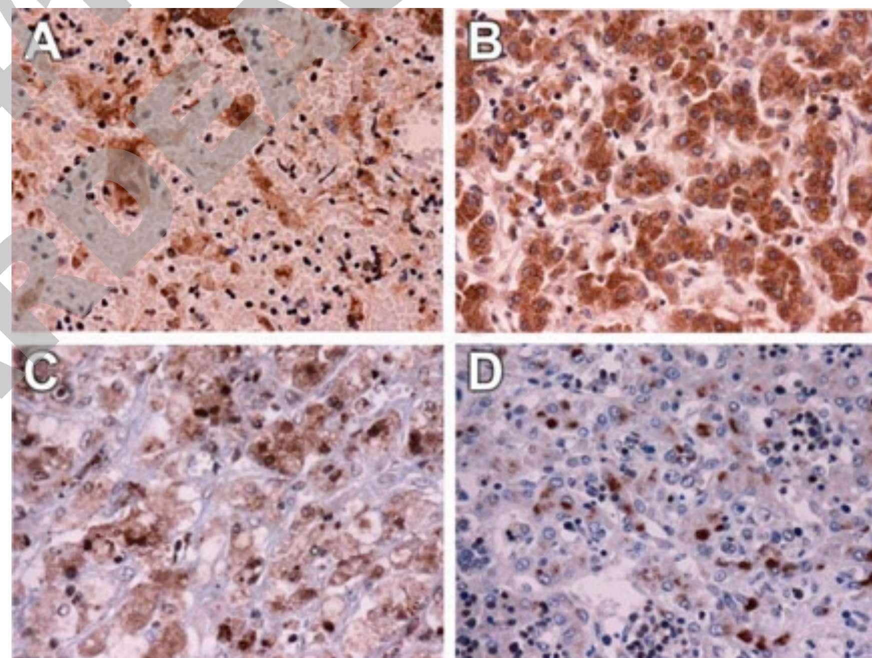
- gestational alloimmune liver disease (GALD)-associated NH (GALD-NH)
- for each case GALD complement-mediated hepatocyte injury can be demonstrated
- Positive C5b-9 immunostaining on the hepatocytes
- GALD is considered to be the most common cause of NH (>95% of cases)

Cb9 immunostaining on hepatocytes

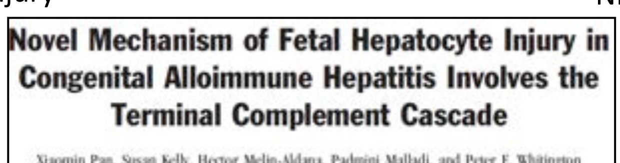
- *Pan X, Kelly S, Melin-Aldana H, Malladi P, Whitington PF. Novel mechanism of fetal hepatocyte injury in congenital alloimmune hepatitis involves the terminal complement cascade. Hepatology 2010;51:2061-68.*
- *Whitington PF, Pan X, Kelly S, Melin-Aldana H, Malladi P. Gestational alloimmune liver disease in cases of fetal death. J Pediatr. 2011 Oct;159(4):612–6.*



Immunohistochemistry for TCC neoantigen in typical cases of NH with subacute and chronic liver injury



Immunohistochemistry for TCC neoantigen in cases of NH with acute liver injury


Novel Mechanism of Fetal Hepatocyte Injury in Congenital Alloimmune Hepatitis Involves the Terminal Complement Cascade

Xiaomin Pan, Susan Kelly, Hector Melin-Aldana, Padmini Malladi, and Peter F. Whitington

GALD : mechanisms of iron overload

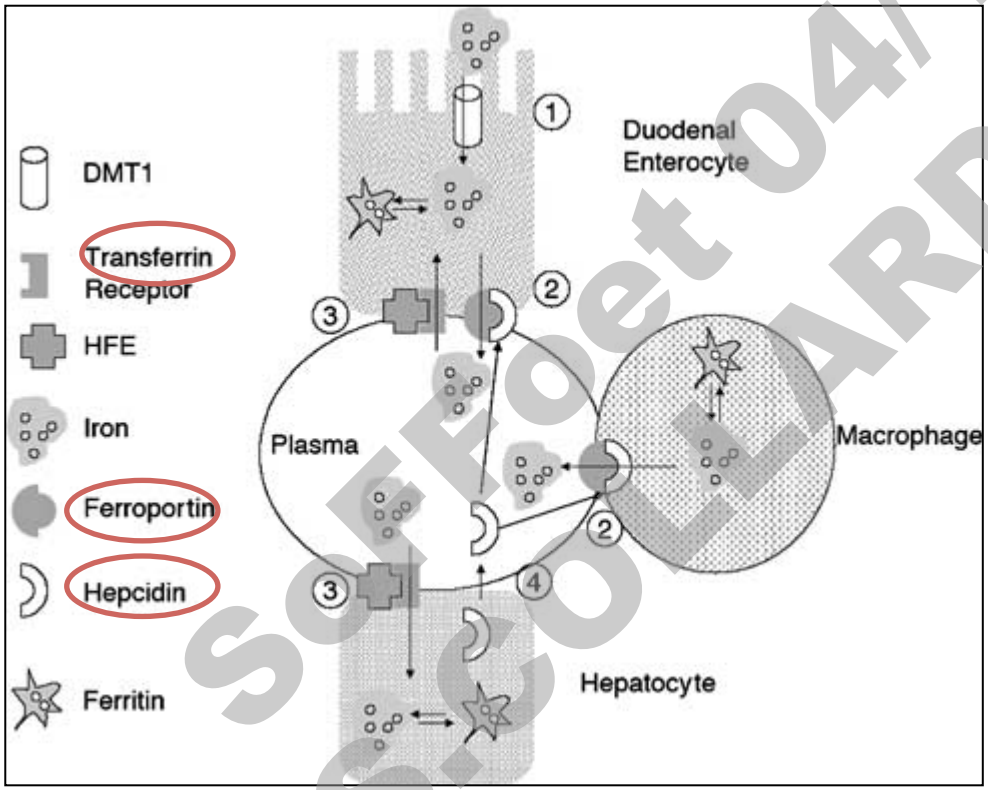
- **Complement-mediated liver injury is the primary event**
- **It is not a primary iron overload disease**
- MAC-mediated cell lysis
- Fetal/neonatal iron overload and siderosis of extrahepatic tissues result from fetal liver dysfunction

Proteins involved in iron homeostasis

Modern Pathology (2007) 20, S31–S39
© 2007 USCAP, Inc All rights reserved 0893-3952/07 $30.00
www.modernpathology.org

Iron overload syndromes and the liver

Kenneth P Batts



Iron homeostasis.
Step 1 represents DMT1-mediated iron absorption into mature enterocytes. Step 2 indicates ferroportin-mediated movement of iron from enterocytes (and macrophages) into the circulation. Step 3 illustrates movement of iron from the circulation into hepatocytes and duodenal enterocytes fostered by the complex of Transferrin receptor 2 and the HFE protein.
Step 4 indicates hepatocyte production and excretion of hepcidin into the circulation. Hepcidin downregulates activity of ferroportin, predominantly in duodenal enterocytes and macrophages (step 2).

GALD: mechanisms of iron overload

- Ferroportin is highly expressed in placental cells
- Hepcidin is produced by the fetal liver and is the main regulator of iron efflux from the placenta
- reduced hepatocyte mass in GALD
  - ↘ hepcidin production
  - impair the feedback control of placental iron flux

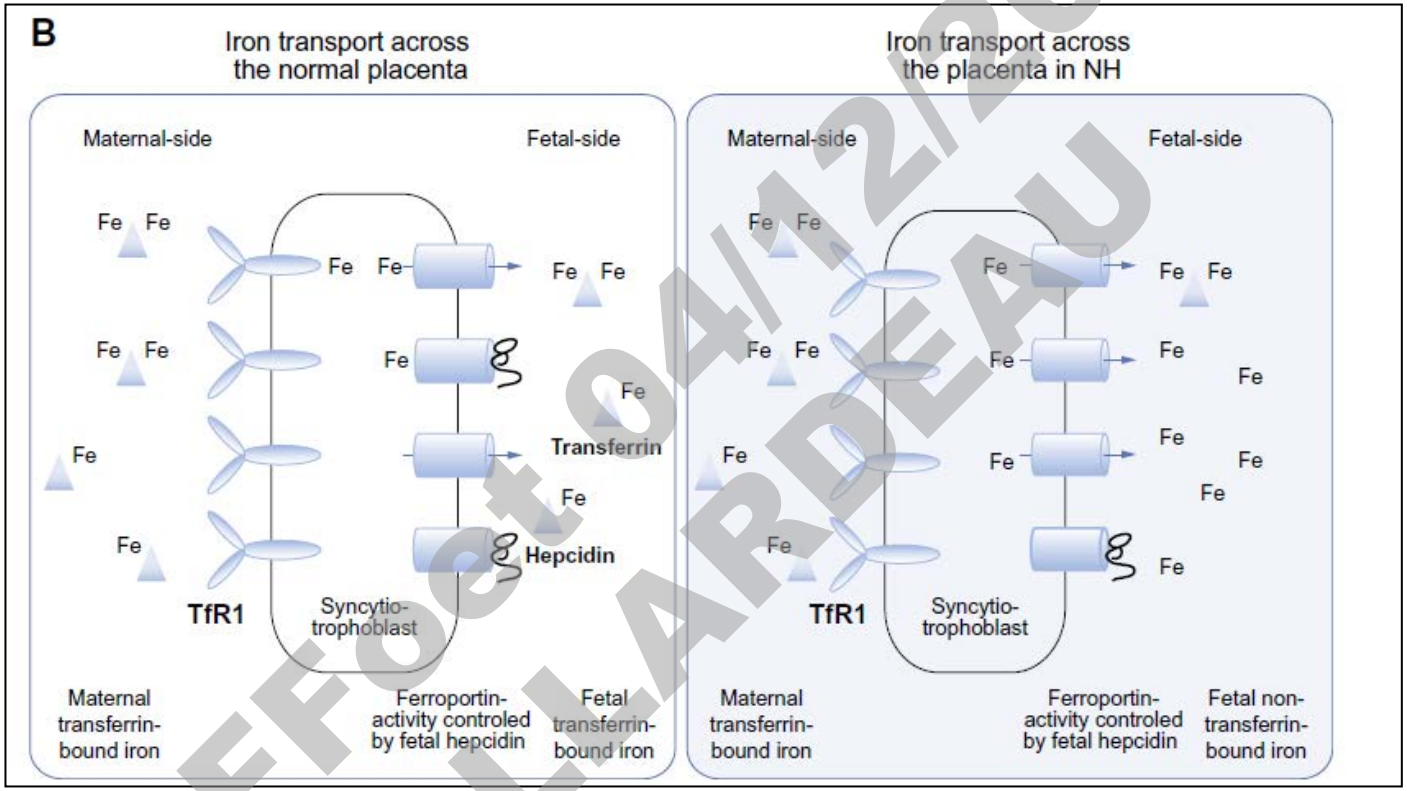
Editorial

EASL JOURNAL OF HEPATOLOGY

Journal of Hepatology 2012 vol. 56 | 1226–1229

Control of iron metabolism – Lessons from neonatal hemochromatosis

Heinz Zoller[1,*], A.S. Knisely[2]



Proposed pathophysiology of neonatal hemochromatosis.
(Left panel) Iron transport across the normal placenta, where maternal transferrin bound iron is taken up through transferrin medicated endocytosis at the apical (maternal) membrane of the syncytiotrophoblast, which is released at the basolateral membrane by ferroportin and binds to fetal transferrin. Iron release is controlled by the fetus through fetal hepcidin, which inhibits ferroportin.
(Right panel) Iron transport across the placenta of a fetus with neonatal hemochromatosis. Reduced fetal hepcidin and reduced transferrin concentration are proposed to result in dysregulated transplacental iron transfer and increased non-transferrin bound iron, which is toxic and primarily stored in tissues with high expression of the transition metal transport protein ZIP14 and low expression of the iron export protein ferroportin.

GALD : extrahepatic hemosiderosis

determined by the tissue's capacity for importing non-transferrin-bound iron (NTBI)

Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Journal of Hepatology 2012

Neonatal iron overload and tissue siderosis due to gestational alloimmune liver disease

Silvana Bonilla†, Joshua D. Prozialeck†, Padmini Malladi, Xiaomin Pan, Songtao Yu, Hector Melin-Aldana, Peter F. Whitington*

Table 3. Expressions of ZIP14 and ferroportin in extrahepatic tissues from infants with GALD as they relate to siderosis.

	Siderosis	ZIP14	Ferroportin
Pancreatic acinar cells	++	+++	+
Thyroid follicle epithelia	++	++	-
Hassall's corpuscles	++	++	+
Myocardium	+	++	++
Adrenal cortex	+	++	+
Renal tubular epithelium	+	+	+
Submucosal salivary glands	++	+++	-

ZIP14 facilitates the uptake of NTBI into various cells

GALD : a spectrum

- fetal acute liver failure and fetal death with or without iron overload
- neonatal liver failure with liver and extrahepatic siderosis
- (antenatal cirrhosis and mild neonatal liver disease without hepatic siderosis)
- mild neonatal liver disease (anomalies of LFT)

Inter and intrafamilial variability

individual sensitivity to alloimmune injury?

begins in utero in all cases (midgestation)

GALD : clinical presentation

EXPERIENCE AND REASON

PEDIATRICS Vol. 116 No. 6 December 2005

Disparate Clinical Presentation of Neonatal Hemochromatosis in Twins

Udeme D. Ekong, MBBS, MRCP; Susan Kelly, RN, BSN; and Peter F. Whitington, MD

2 sets of twins (1 set without pregnancy immunotherapy): 1 infant with liver failure and the other nearly unaffected (elevated serum AFP and/or ferritin levels)

Neonatal Liver Cirrhosis Without Iron Overload Caused by Gestational Alloimmune Liver Disease

Debray FG, de Halleux V, Guidi O, Detrembleur N, Gaillez S, Rausin L, Goyens P, Pan X, Whitington PF.

Pediatrics. 2012 Apr;129(4):e1076-9

34.5 weeks of gestation
no liver or extrahepatic siderosis (liver biopsy and MRI)
But antiplatelet antibodies in the mother's serum→ **fetal alloimmune thrombopenia**

GALD : clinical presentation

- panethnic distribution
- sexe ratio ≈1
- Mother: previous fetal or neonatal loss
- No consanguinity
- **Antenatal manifestations**: in late second or third trimester
  - IUGR, oligohydramnios, hydrops, hepatomegaly, ascites
    → fetal death, stillbirth and prematurity
- **Neonatal manifestations**:
  - Liver failure usually within the first hours of life → multiorgan failure→ death
- Without treatment: very poor prognosis

GALD: Laboratory tests

- **Liver failure**
  - severe coagulopathy :↑ INR (normal range in newborns: 0.8–1.5)
  - hyperammonemia (>95 umol/L)
  - hypoglycemia
  - hypoalbuminemia
- **Liver function test**
  - Transaminases and γGT: N or mildly ↑
  - ↑ AFP >100 000 ng/mL (normal values in term newborns <80 000 ng/mL)
  - ↑direct and indirect bilirubin
- **Iron overload**
  - ↑ ferritin (normal values 40–775 ng/mL)
  - hypersaturation (up to 95–100%) of the available transferrin
- Severe **thrombocytopenia** (platelet count <50 000 µL) +/- anemia

GALD : clinical & biological presentation

- **nonspecific and may mimic**
  - viral or bacterial **infections** but negative infectious work-up
  - **perinatal asphyxia :** low Apgar scores **+**respiratory distress syndrome + premature neonates , tachypnea, pulmonary hypertension, pulmonary hemorrhage
  - **disseminated intravascular coagulopathy (DIC):**consumption of clotting factors and platelets+ schistocytes + severe bleeding
  - **haemolytic-uraemic syndrome (HUS):** acute oligo-anuric renal failure + anemia with fragmented red blood cells (schistocytes)+ thrombocytopenia
  - **metabolic disorders**
  - congenital hepatic arteriovenous malformation: patent ductus venosus + DIC

- **liver failure and hyperferritinemia are not pathognomonic for NH**

  present in other causes of fulminant liver

Pediatr Radiol (2009) 39:823–827
DOI 10.1007/s00247-009-1294-6

ORIGINAL ARTICLE

Neonatal hemochromatosis and patent ductus venosus: clinical course and diagnostic pitfalls

Andy Tsai · Harriet J. Paltiel · Laureen M. Sena · Heung Bae Kim · Steven J. Fishman · Ahmad I. Alomari

LIVER TRANSPLANTATION 20:124, 2014

A.S. Knisely, M.D

LETTER TO THE EDITORS

Patent Ductus Venosus and Acute Liver Failure in the Neonate: Consider Neonatal Hemochromatosis With Liver Scarring

Doppler ultrasound : patent ductus venosus

- in the setting of portal hypertension
- mistaken for a congenital hepatic arteriovenous shunt

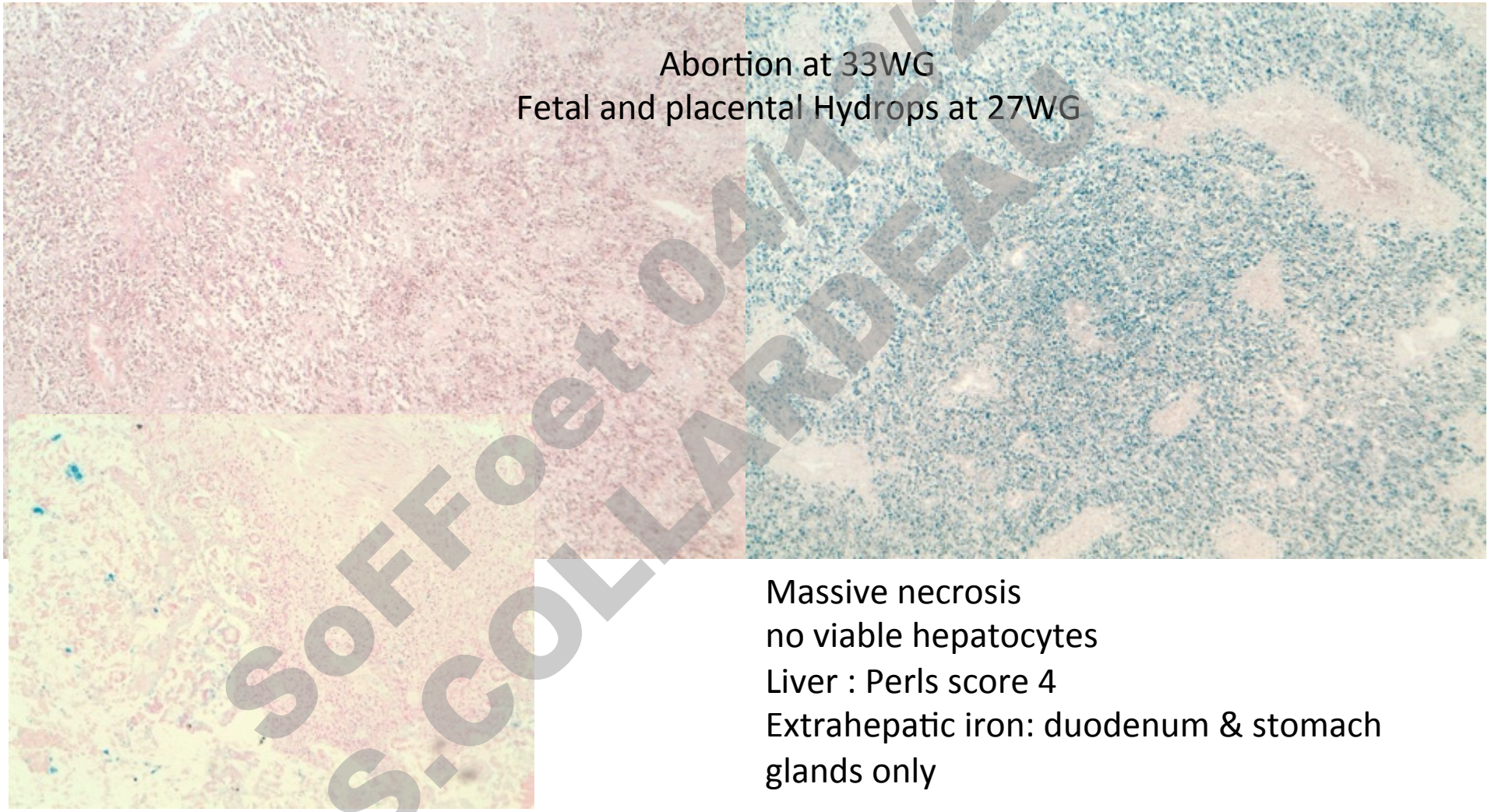
GALD: pathological findings

acute hepatocyte injury

- fetal acute liver failure and fetal death
- Small proportion of GALD cases
- with or without iron overload: extrahepatic siderosis might not have time to develop
- Liver injury:
  - Global panlobular hepatocyte necrosis
  - no or minimal fibrosis
  - no viable hepatocytes
  - only ‘‘ghosts’’ remained
  - Absent hepatic cords
  - # postmortem hepatocyte autolysis in which cords remain

Whitington PF, Pan X, Kelly S, et al. Gestational alloimmune liver disease in cases of fetal death. J Pediatr 2011;159:612–16

GALD : pathological findings acute hepatocyte injury



Abortion at 33WG
Fetal and placental Hydrops at 27WG

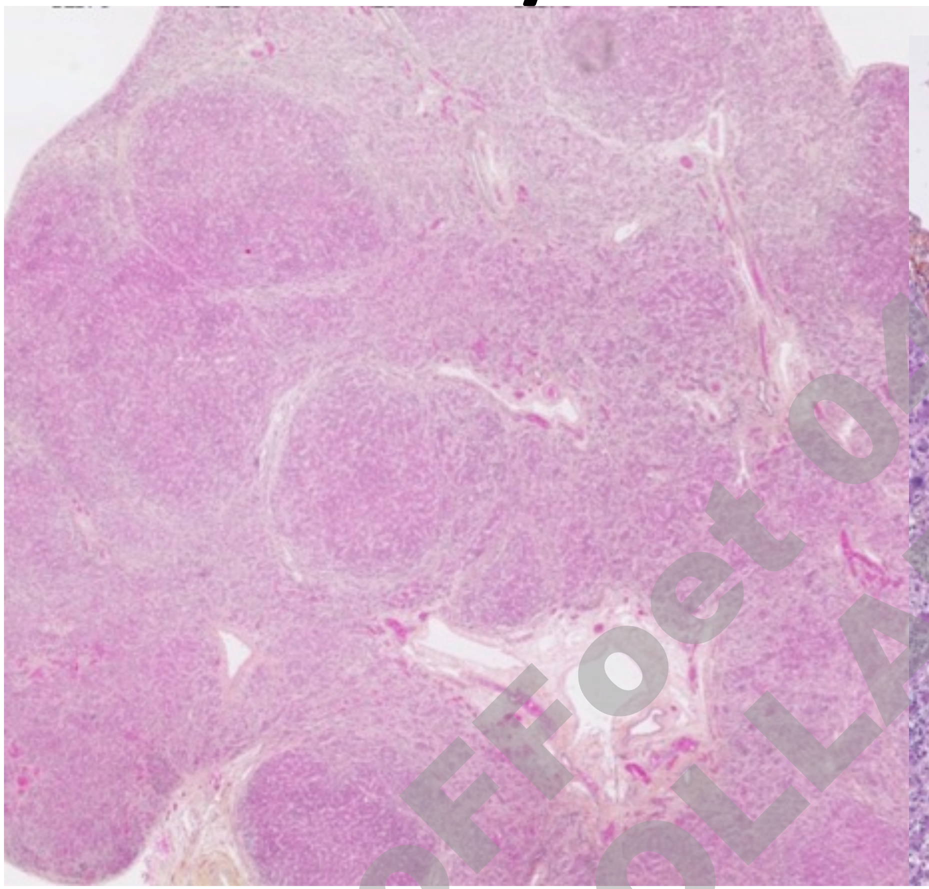
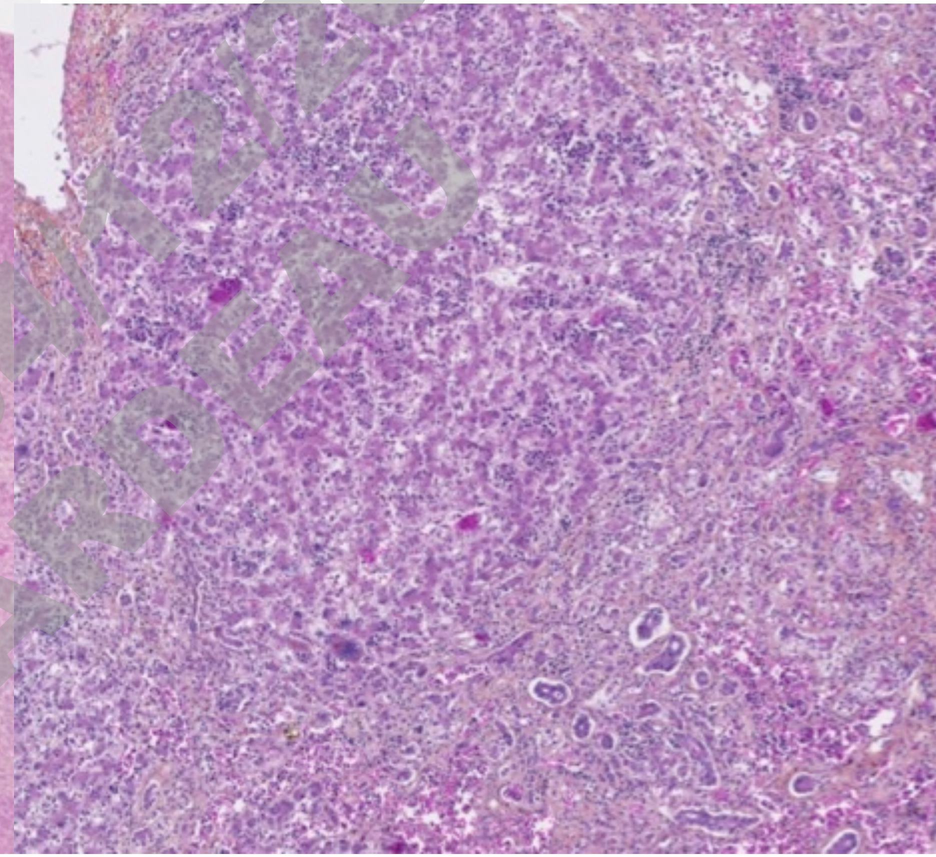
Massive necrosis
no viable hepatocytes
Liver : Perls score 4
Extrahepatic iron: duodenum & stomach glands only

GALD: pathological findings

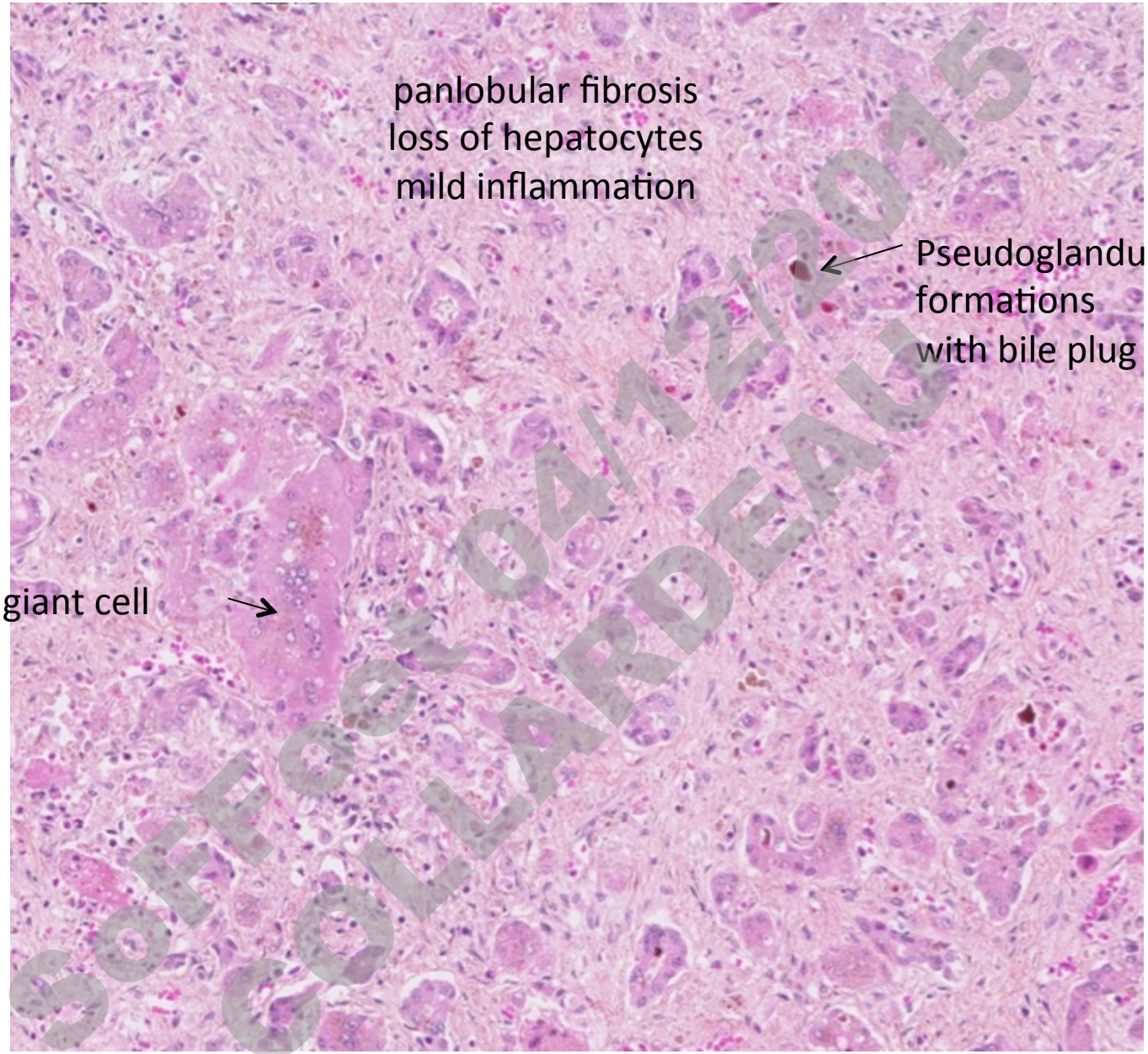
subacute or chronic liver disease

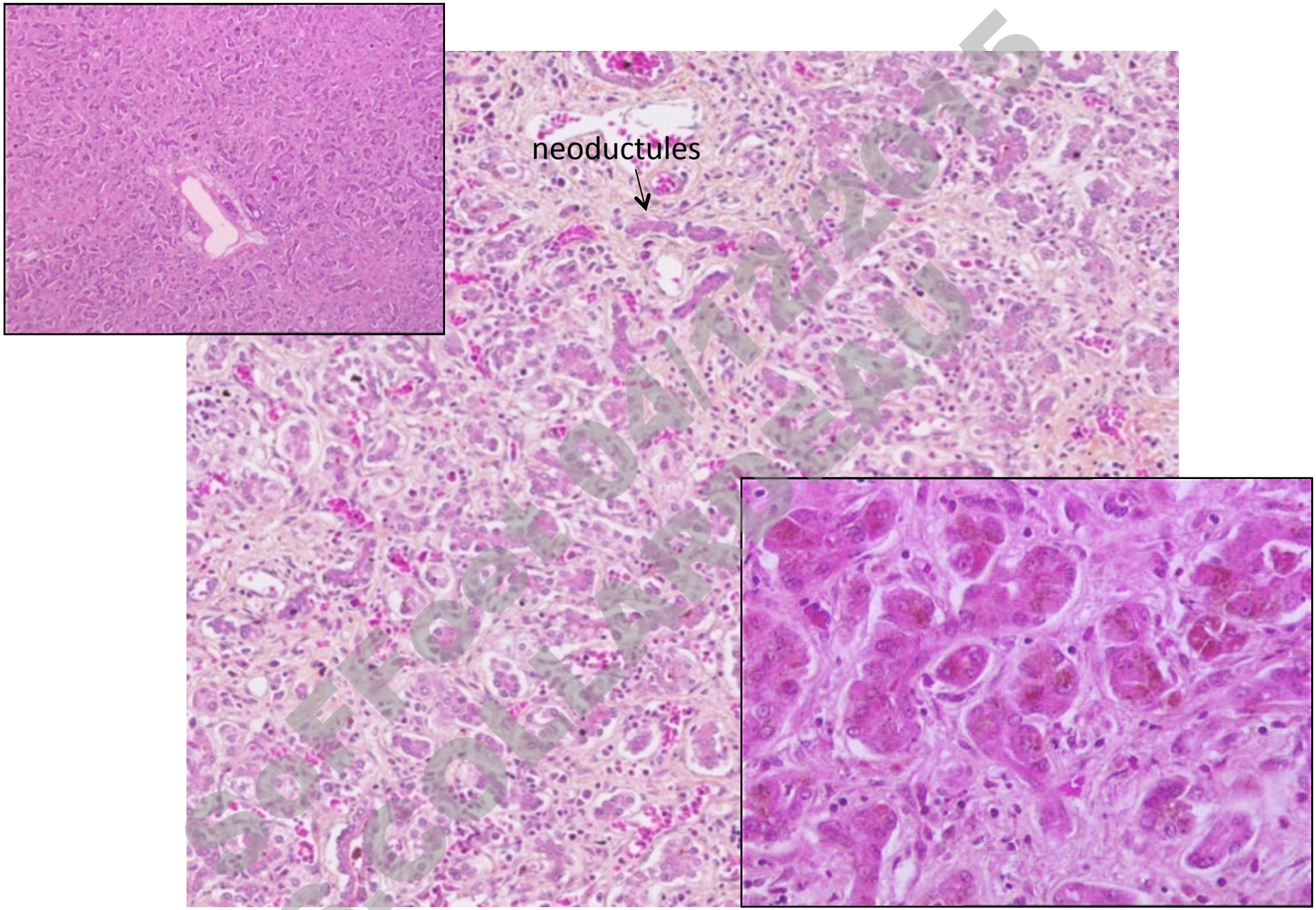
- in most cases, the process moves more slowly
- starting in midgestation: fetus and neonates
- extrahepatic siderosis present
- Liver injury:
  - extensive fibrosis with mild inflammation
  - loss of hepatocytes
  - surviving cells show
    - giant cell
    - or pseudoglandular transformation and varying degrees of cholestasis
    - tubular forms devoid of bile, similar to “ductular reaction” neoductules or neocholangioles
  - focal nodular regeneration
  - most of the iron deposition in the hepatocytes

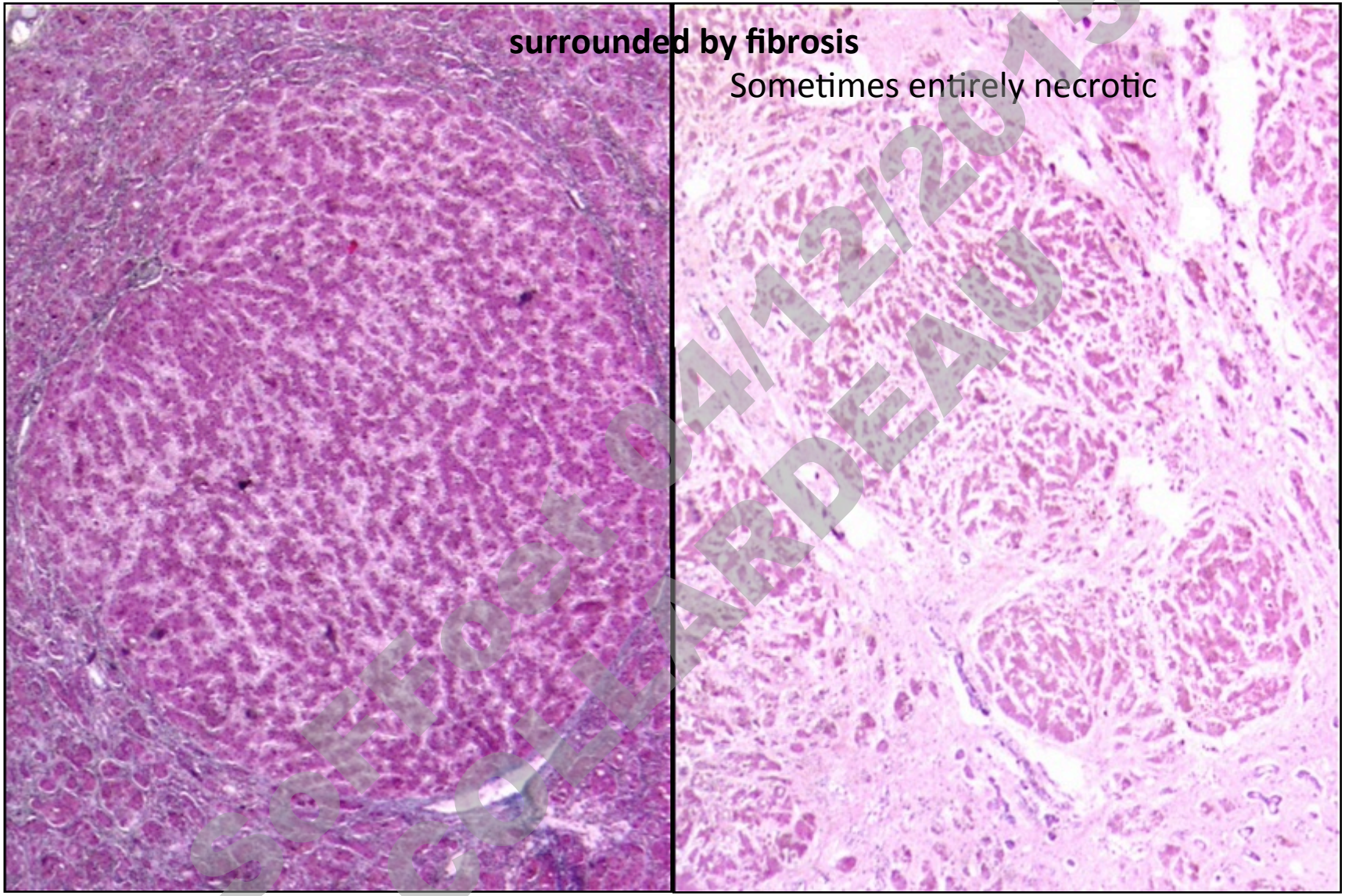
GALD : pathological findings subacute/chronic hepatocyte injury

Heterogeneous
Areas with extensive fibrosis and variable nodules

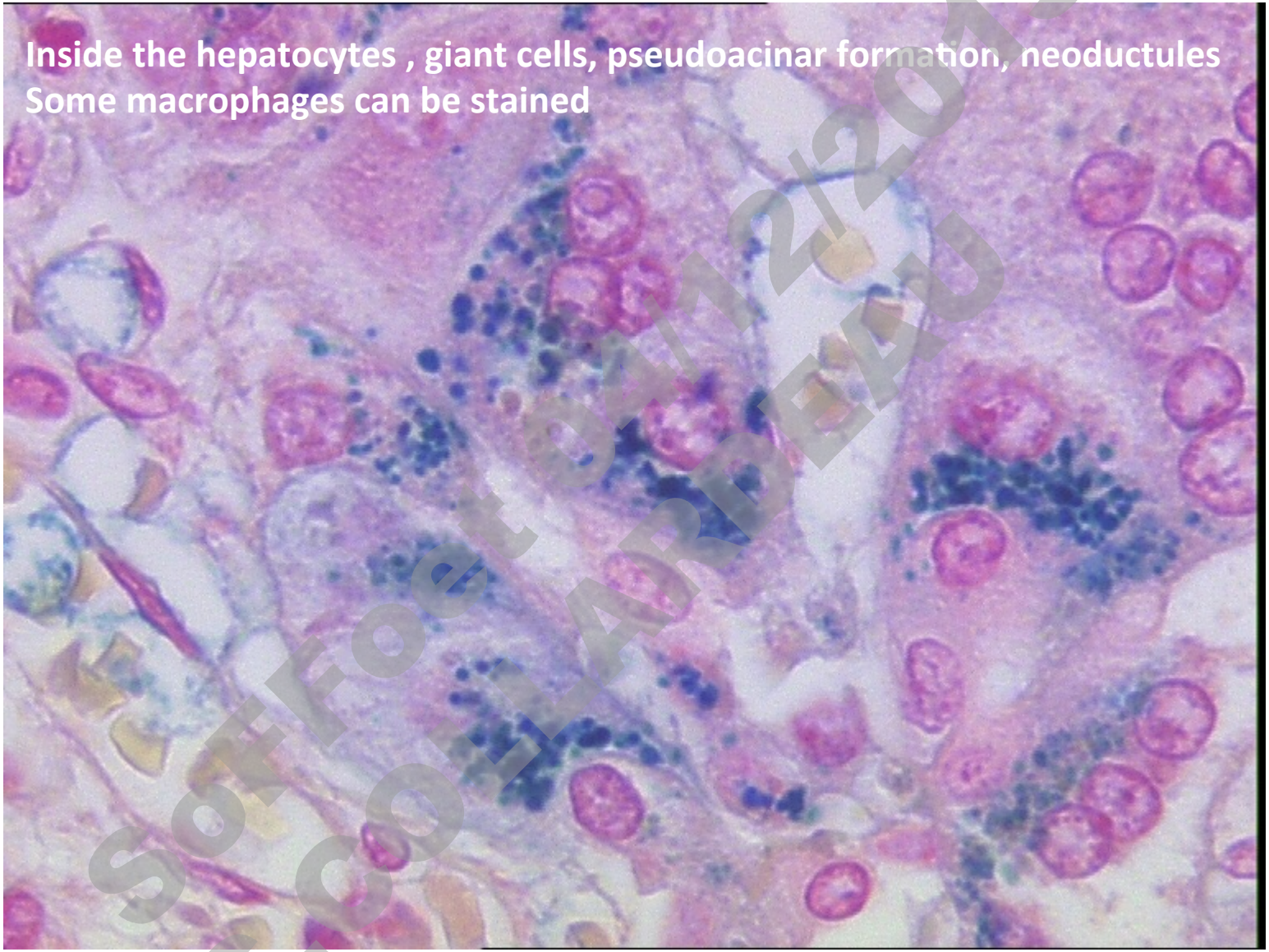




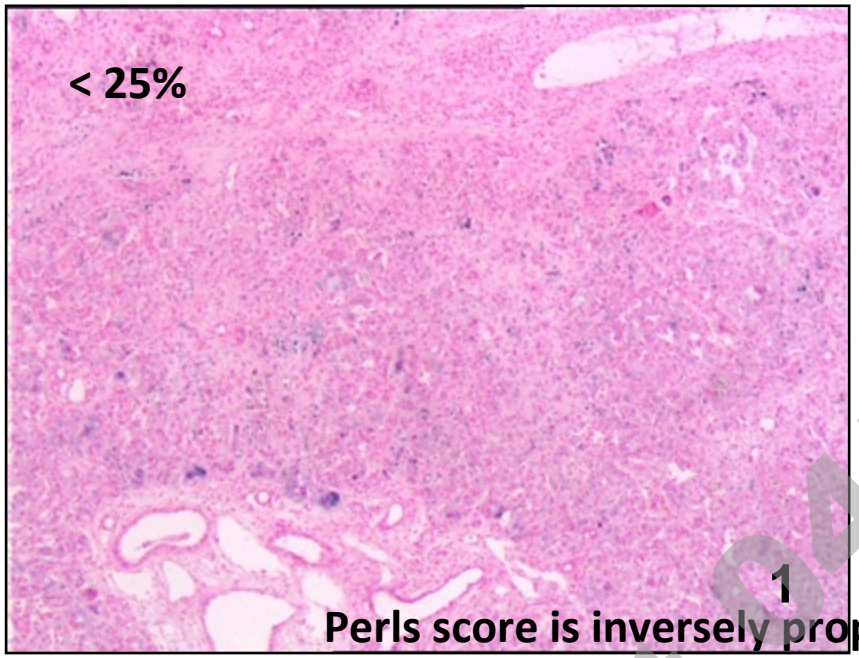


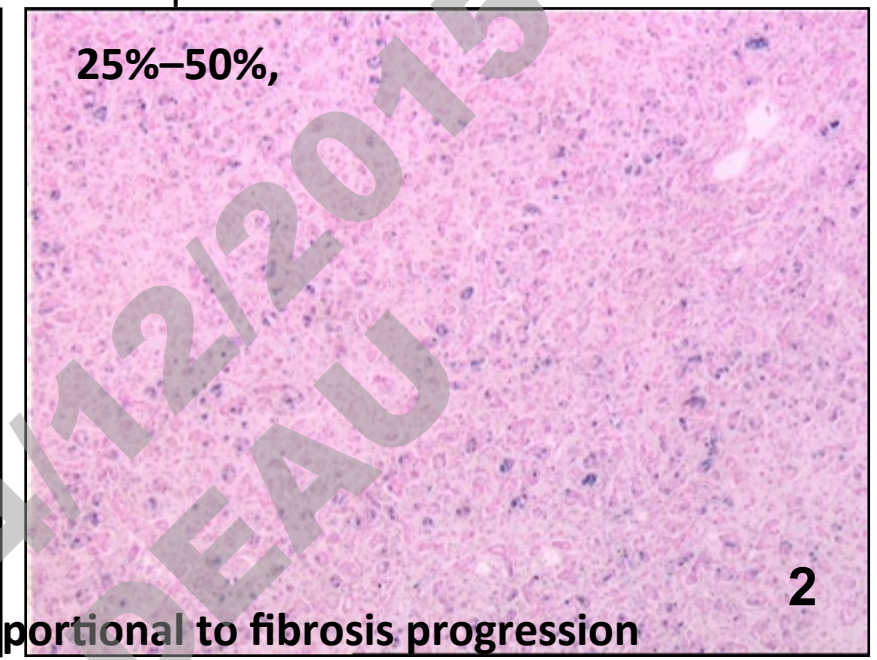
Nodular formation: focal nodular regeneration or areas of preserved hepatocytes?

Liver iron overload

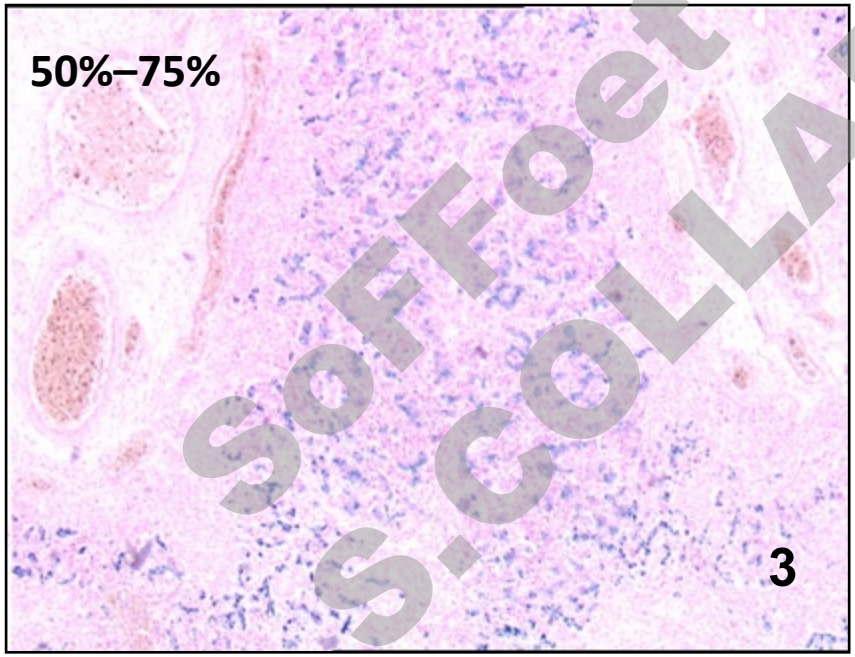


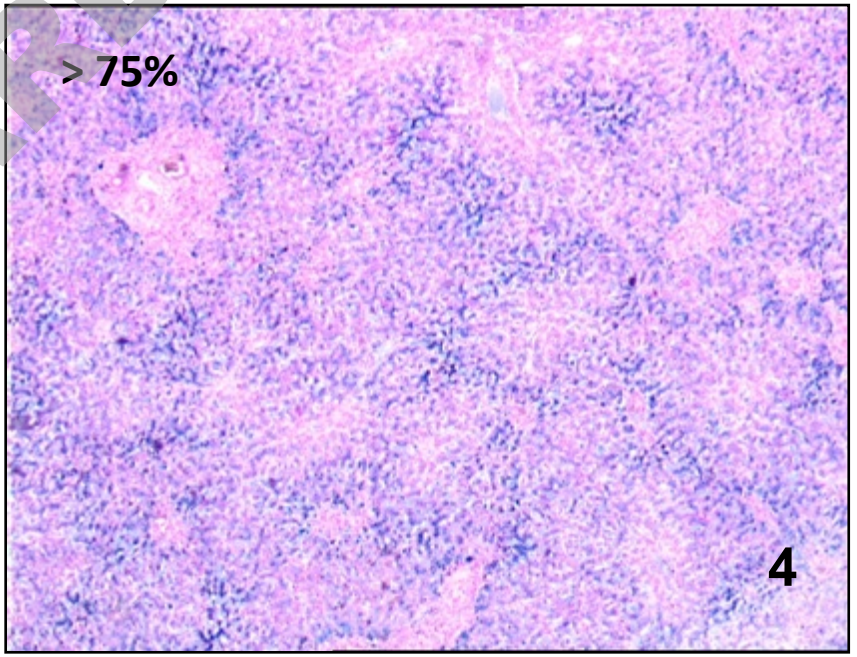
Liver iron overload: Perls semiquantitative score

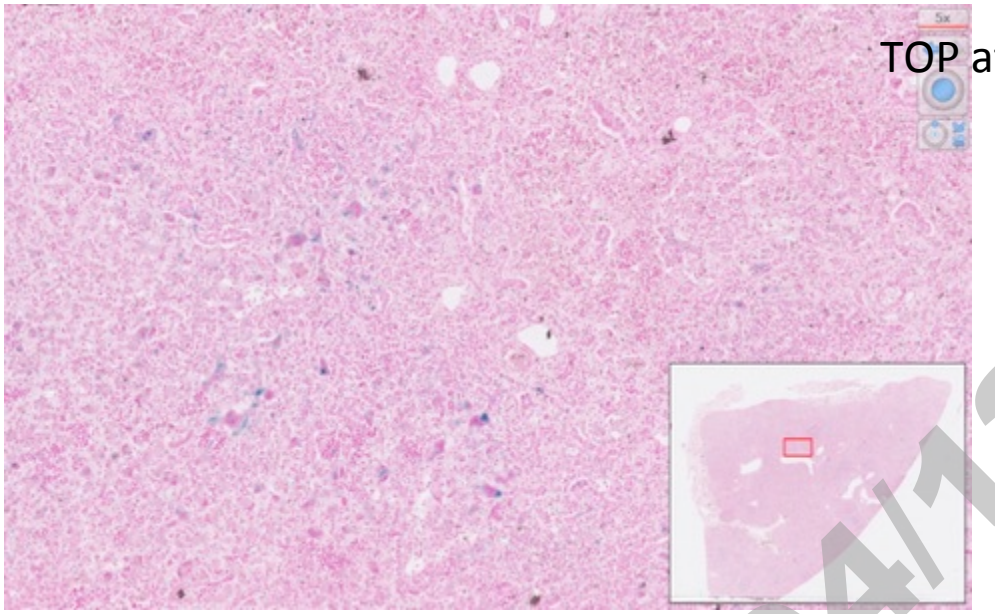




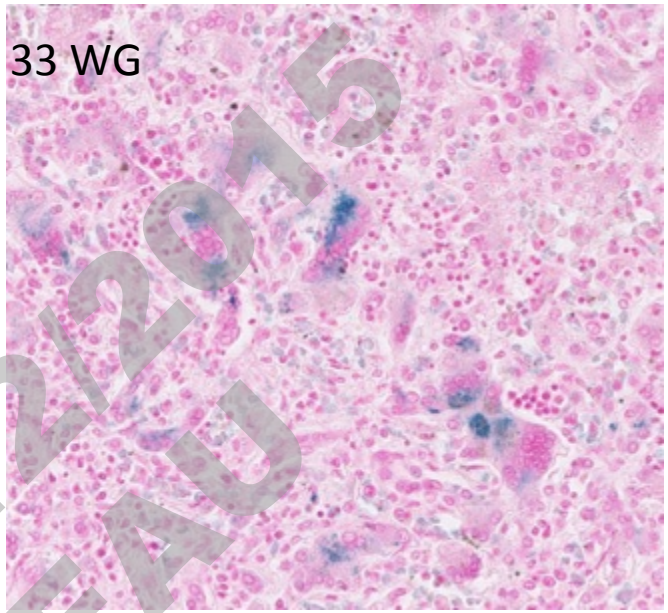
Perls score is inversely proportional to fibrosis progression

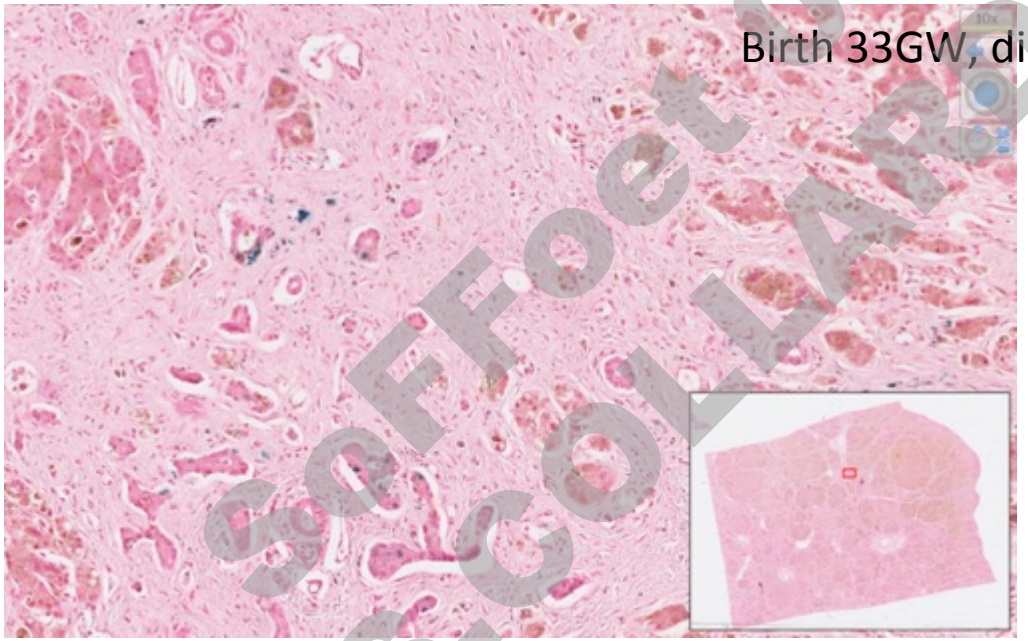




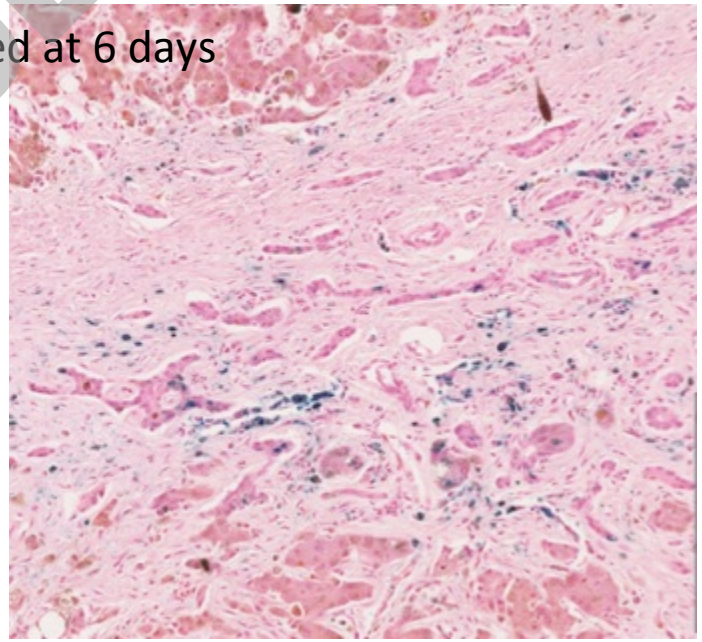


TOP at 33 WG

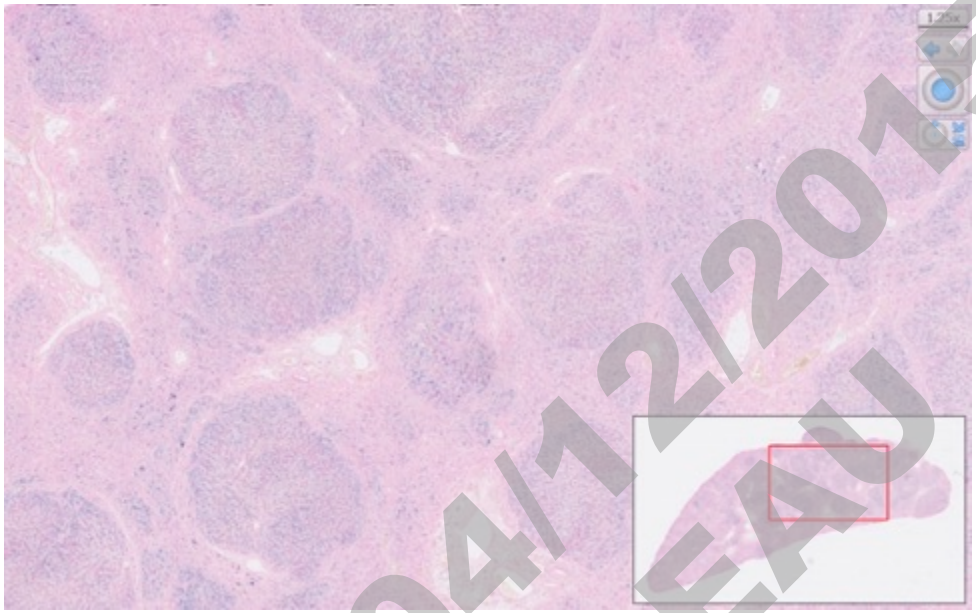


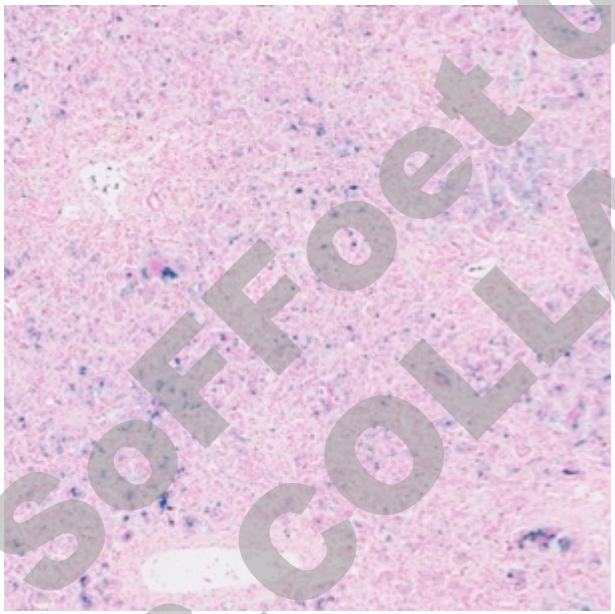


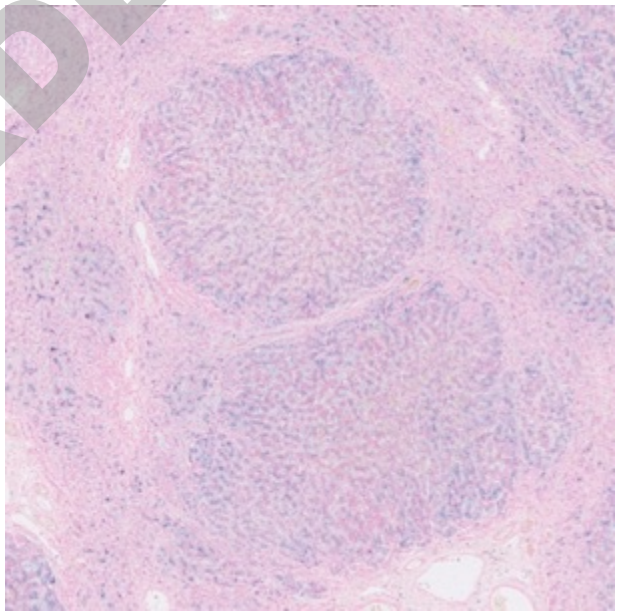
Birth 33GW, died at 6 days



Birth : 30GW
Died at 5 days







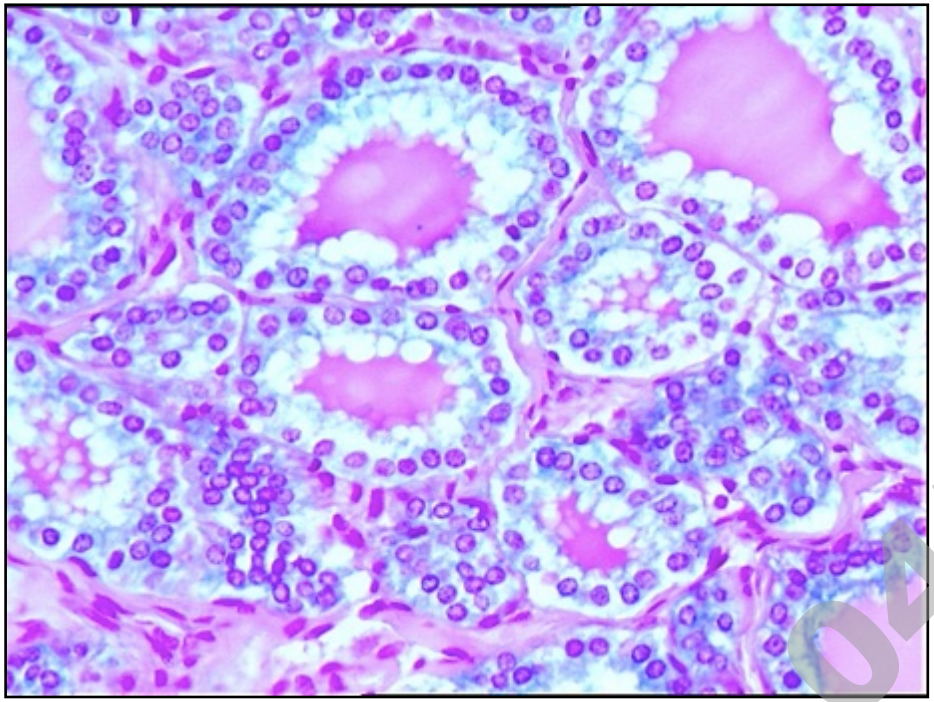
Extrahepatic iron overload

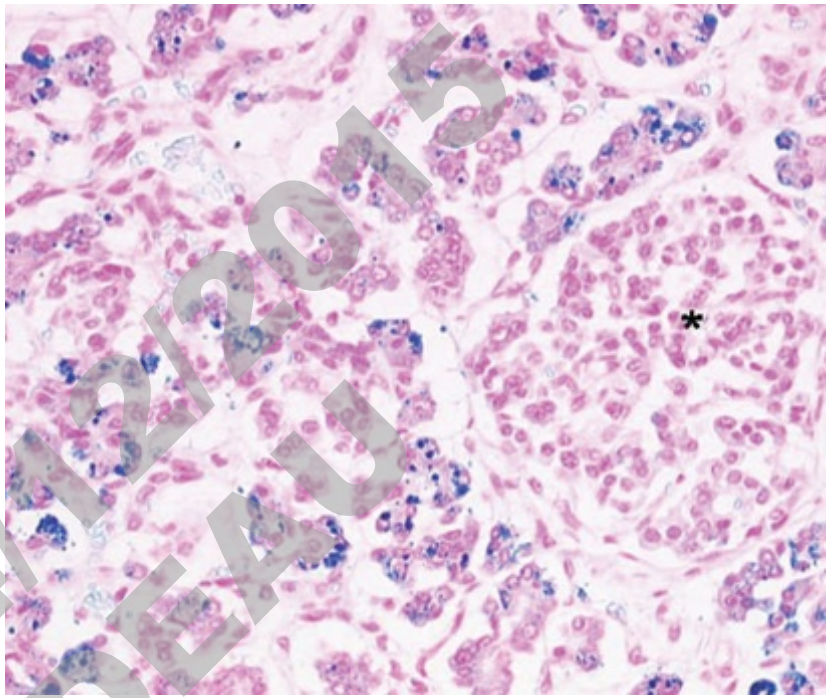
- **acinar cells of the pancreas**
- acinar cells of minor salivary glands
- proximal renal tubules
- **thyroid follicles**
- adrenal cortex
- myocardium
- parathyroid
- pituitary gland
- Hassal's corpuscles
- Digestive glands

Extrahepatic iron storage is only seen after Perls staining

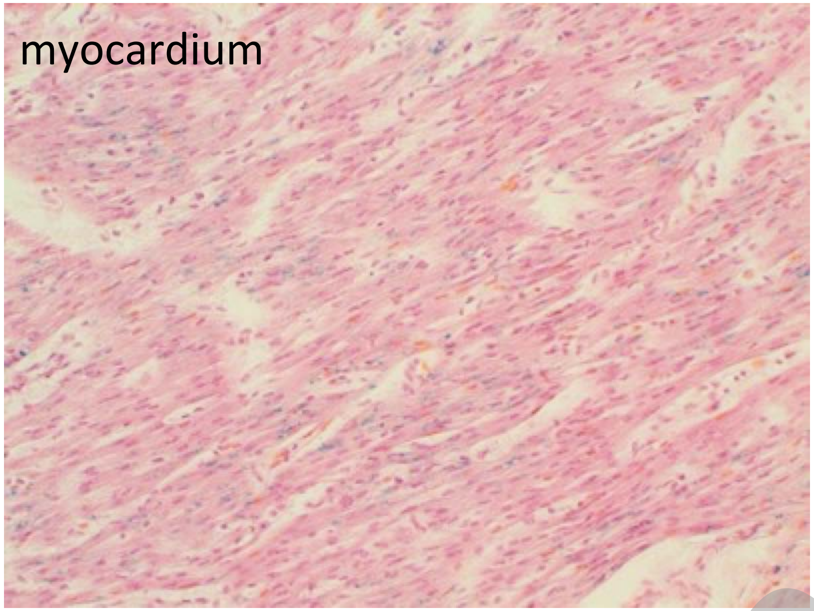
localization varied:
- depending on the age
- within the same sibship

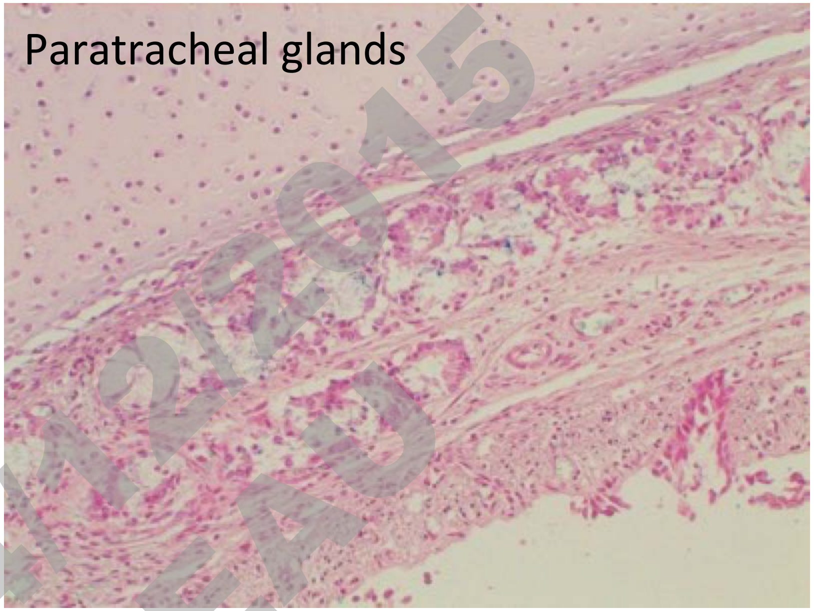
Sometimes:
- **only seen in a few organs**
- **with a mild intensity** (high-power magnification is required)

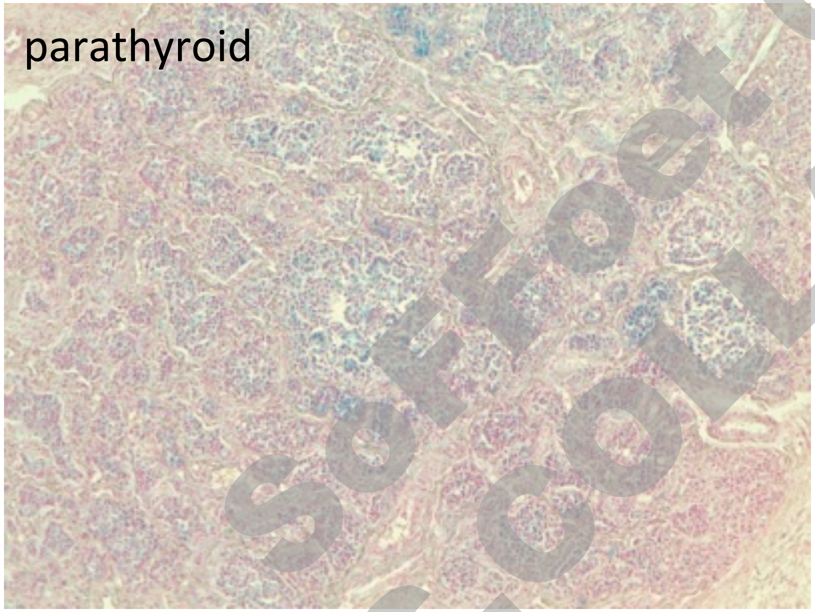


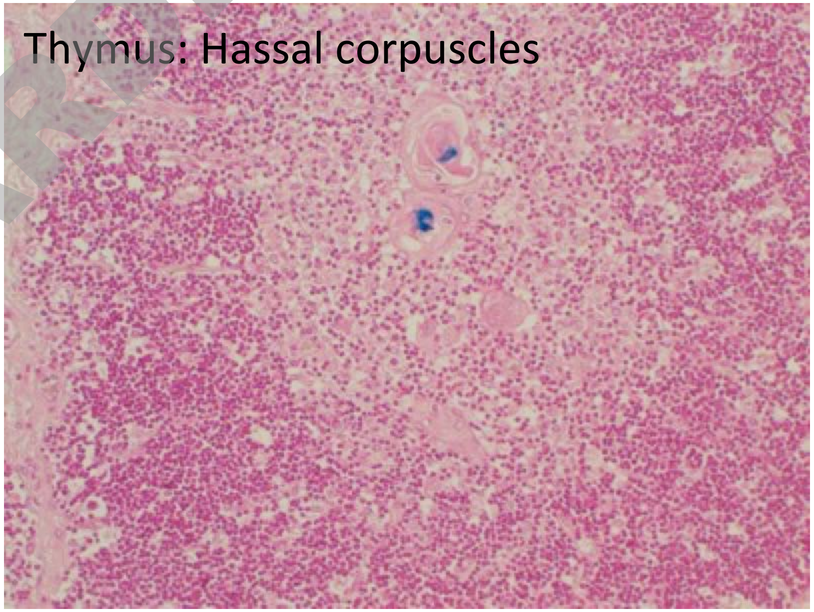


In fetuses: more frequent in thyroid than in pancreas
In neonates: more frequent in pancreas than in thyroid









GALD: other lesions

Hypoperfusion & ischemic lesions

Renal tubular dysgenesis : 30% of our series

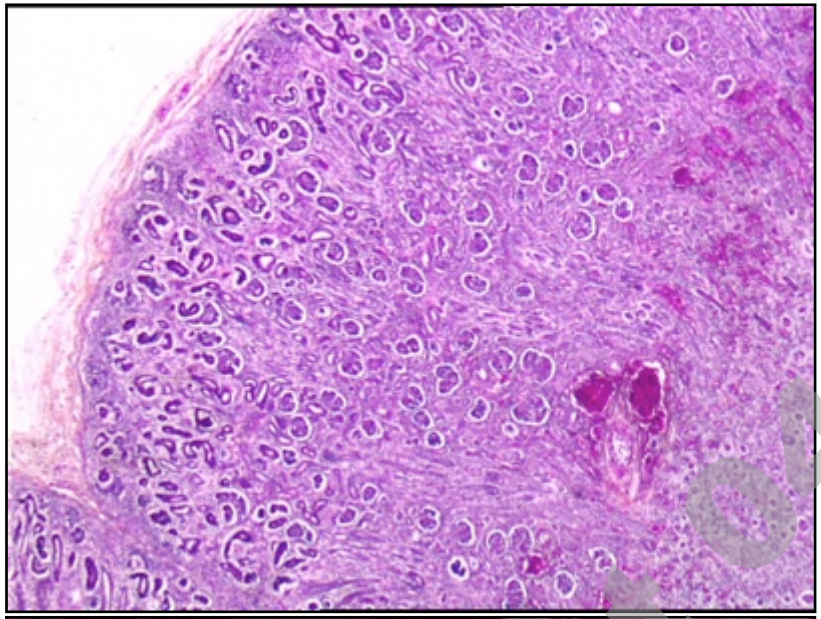
- reduced hepatocyte mass
- ↘ hepatic angiotensinogen
- proximal renal tubular development

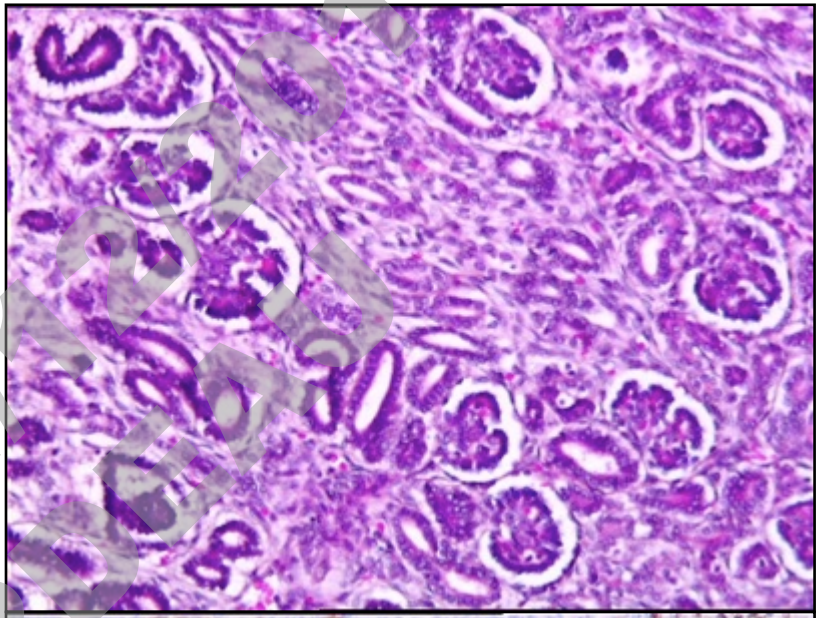
Other renal ischemic lesions:

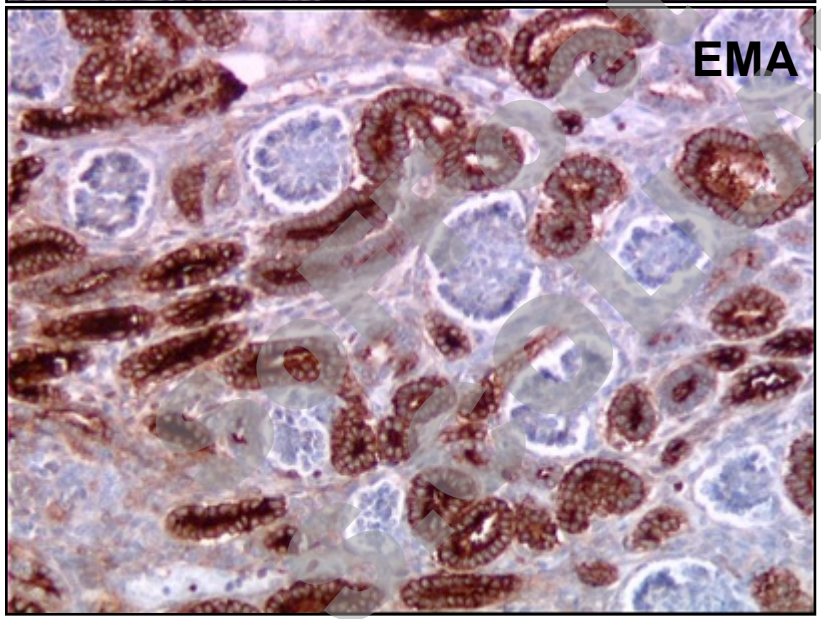
- collapse of glomerular tufts with enlargement of the urinary space often associated with renal tubular dysgenesis

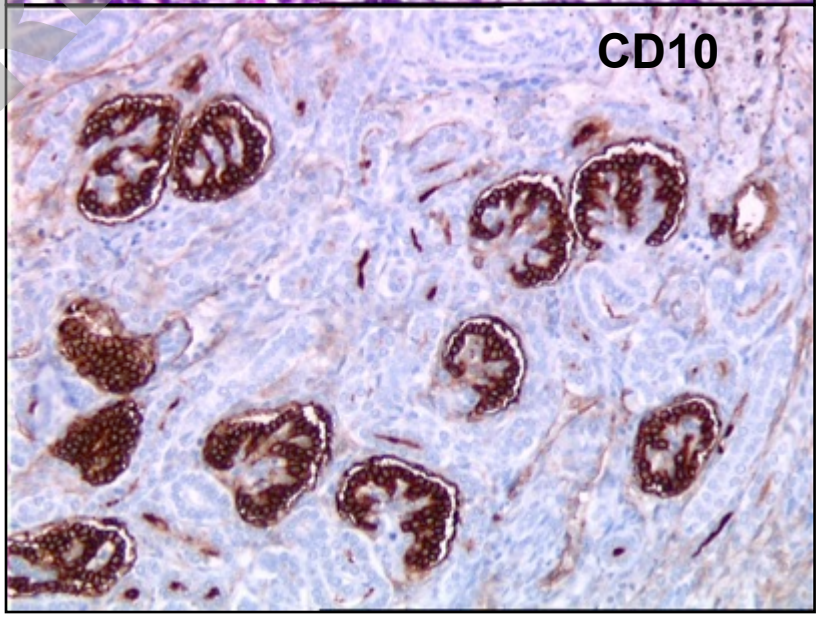
- *Bonilla SF, Melin-Aldana H, Whitington PF. Relationship of proximal renal tubular dysgenesis and fetal liver injury in neonatal hemochromatosis. Pediatr Res 2010;67:188–193.*
- *Azar D, Bonilla S, Amaro D, Whitington P, Krous H. Reduced angiotensinogen in neonatal hemochromatosis leads to impaired development of proximal renal tubules and compensatory glomerular changes. Lab Invest 2011;91:357A.*

Renal tubular dysgenesis : absence or paucity of proximal tubules

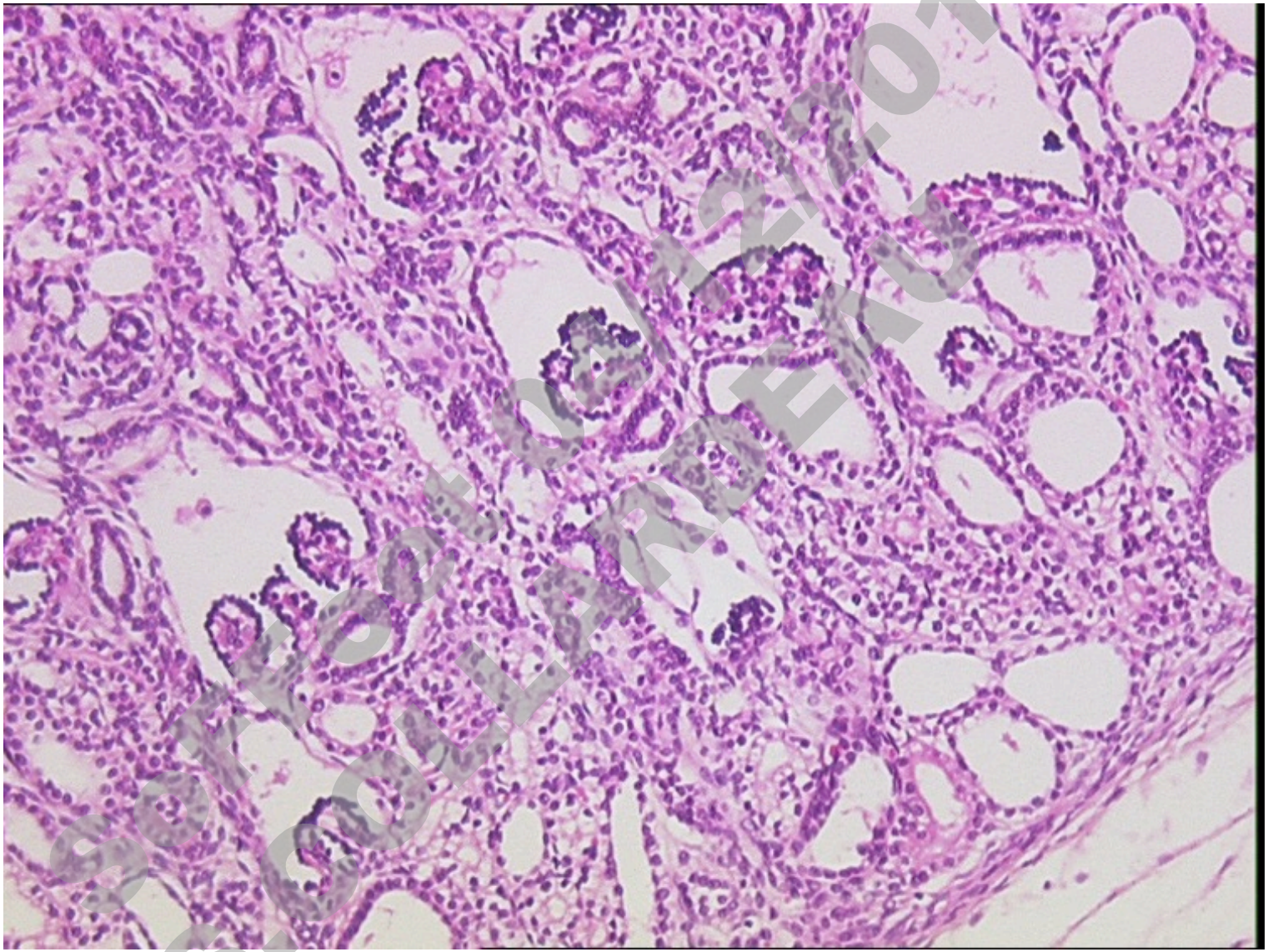






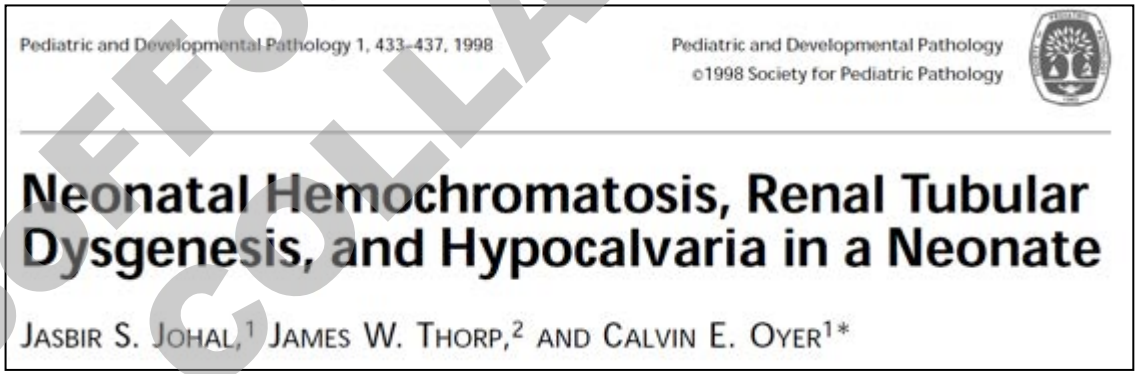


Renal tubular dysgenesis and collapse of glomerular tufts



GALD: other lesions

- **Hypoperfusion & ischemic lesions**
  - hypocalvaria
  - microcephaly
  - with cerebral ischemia



Pediatric and Developmental Pathology 1, 433–437, 1998

Pediatric and Developmental Pathology
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Neonatal Hemochromatosis, Renal Tubular Dysgenesis, and Hypocalvaria in a Neonate

JASBIR S. JOHAL,[1] JAMES W. THORP,[2] AND CALVIN E. OYER[1]*

GALD: other lesions

Chronic fetal distress

thymic hypoplasia

Oligohydramnios sequence

pulmonary hypoplasia
arthrogryposis
facial dysmorphism

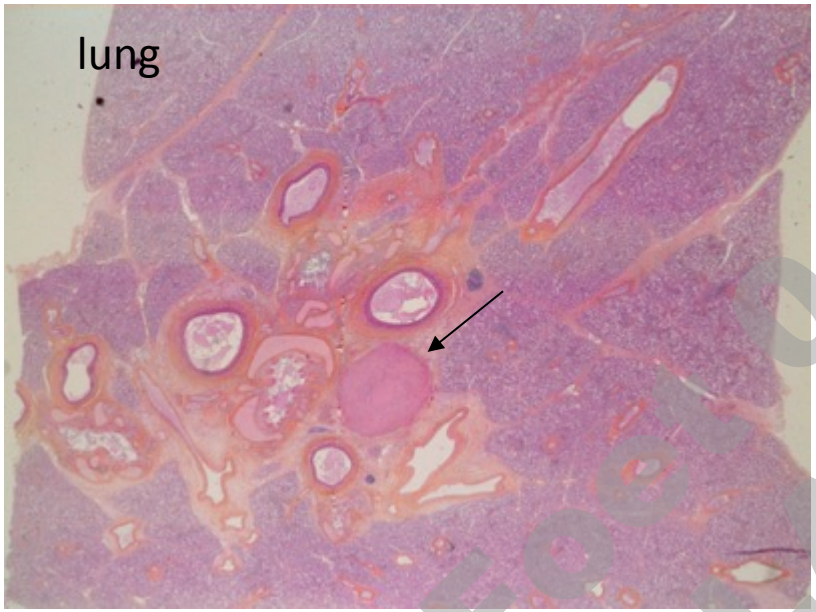
Portal hypertension

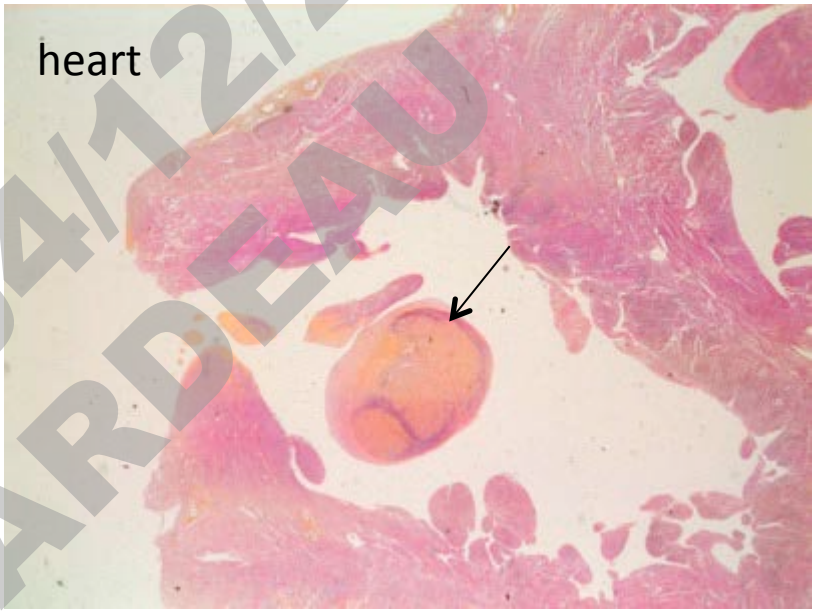
splenomegaly
patent ductus venosus

Extrahepatic hematopoiesis due to liver failure

GALD: other lesions

Myofibroma: 3 cases reported in the litterature





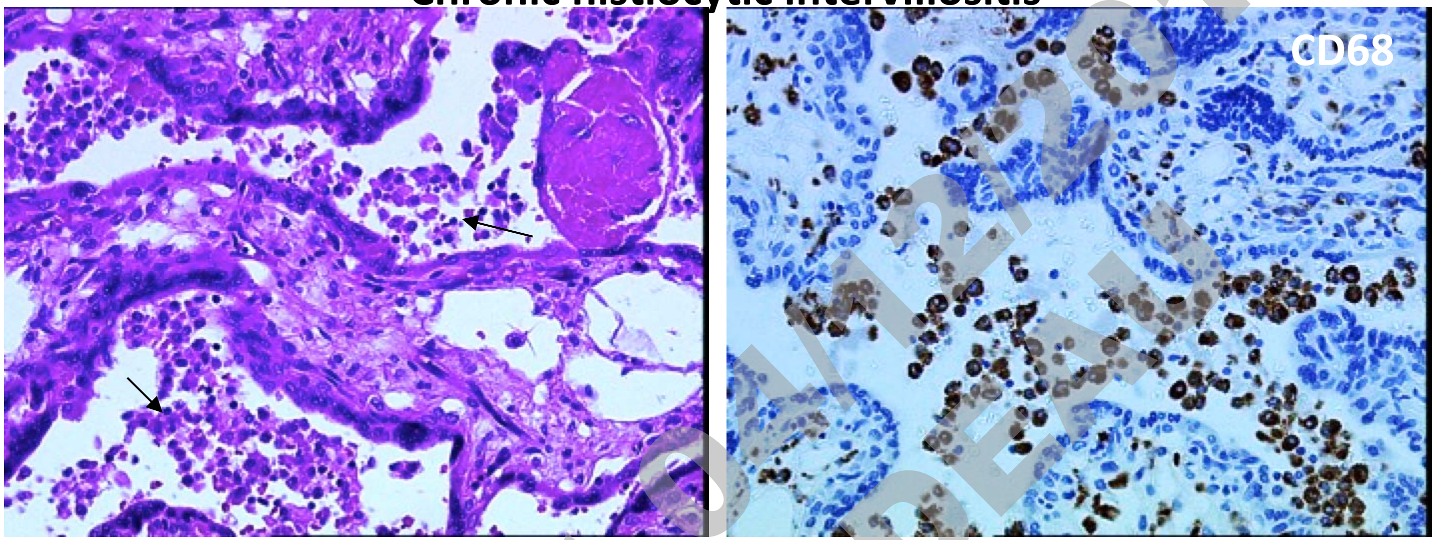
Aksoy F, Go¨ksel S, Ilvan S, Dervis¸og˘lu S, Ramazanog˘lu R. Congenital generalized infantile myofibromatosis and neonatal hemochromatosis: an autopsy case report. Turk J Pediatr 2000;42:334–337.

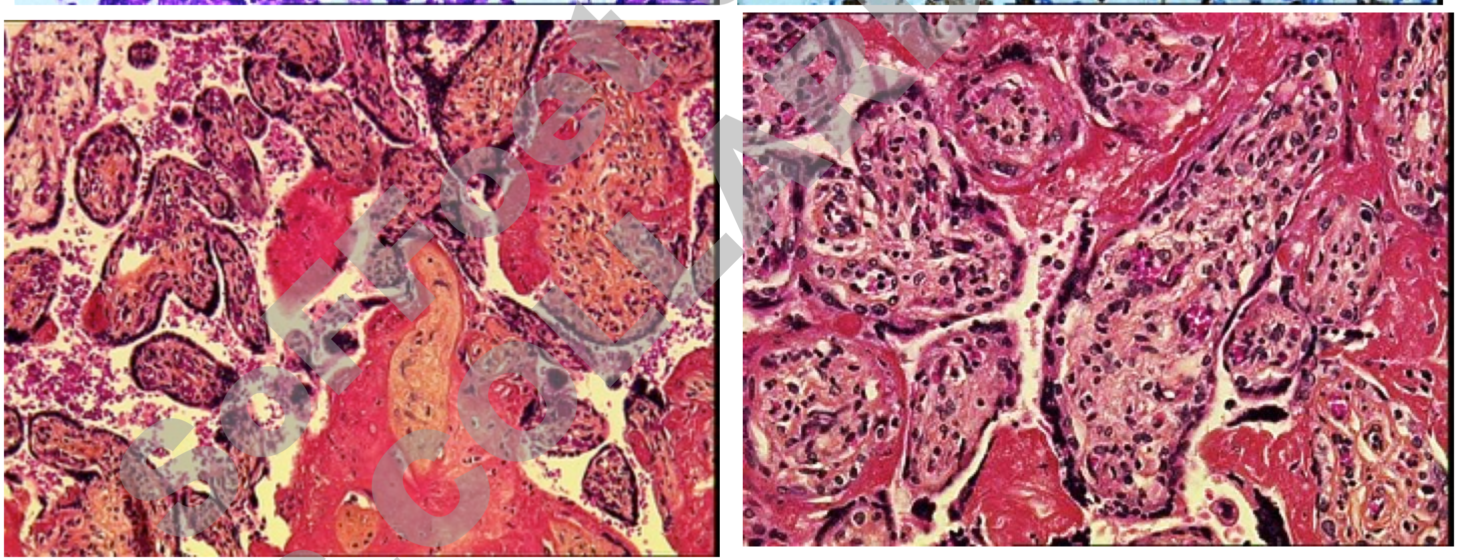
Dalhoj J, Kiaer H, Wiggers P, Grady RW, Jones RL, Knisely AS. Iron storage disease in parents and sibs of infants with neonatal hemochromatosis: 30-year follow-up. Am J Med Genet 1990;37: 342–345.

Collardeau-Frachon S, Heissat S, Bouvier R, Fabre M, et al. French retrospective multicentric study of neonatal hemochromatosis: importance of autopsy and autoimmune maternal manifestations. Pediatr Dev Pathol. 2012;15:450-70.

GALD: other lesions: placenta

Chronic histiocytic intervillositis





Chronic villitis, some avascular villi, perivillous fibrin deposition

GALD: diagnosis

should be suspected :

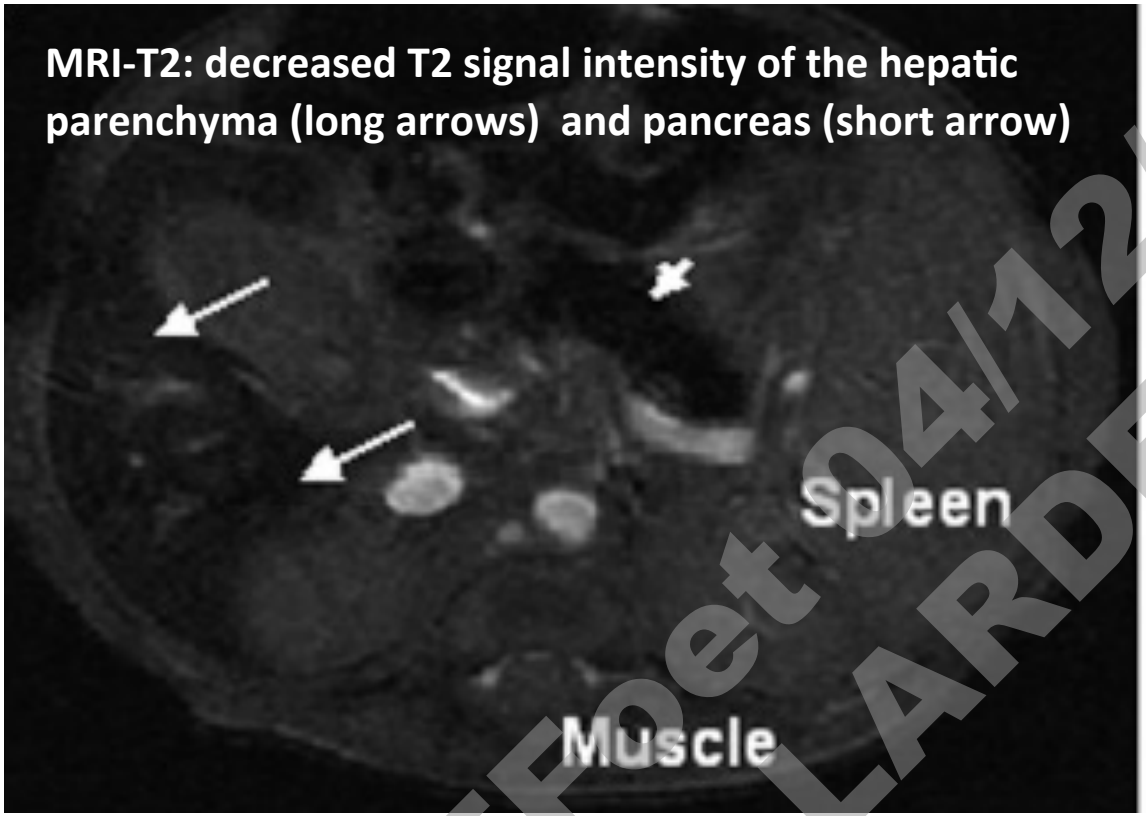
- in all neonates with antenatal or postnatal signs of severe liver disease
  - growth restricted
  - born prematurely
- unexplained fetal demise
  - unexpected intrauterine fetal death in the late-second and third trimester

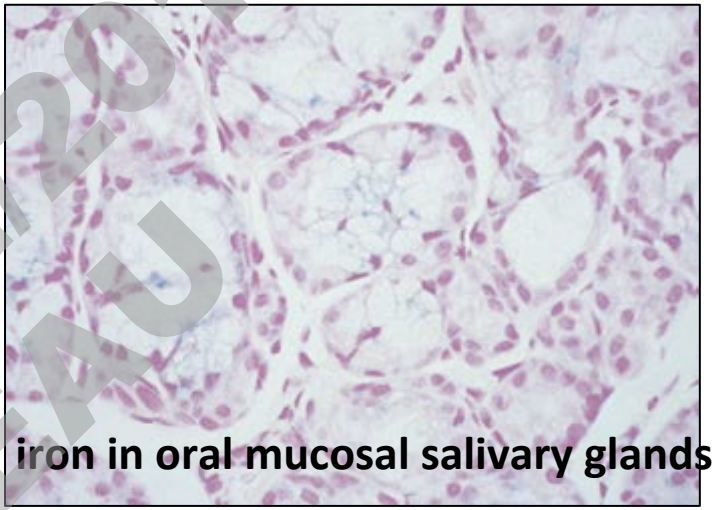
GALD: diagnosis

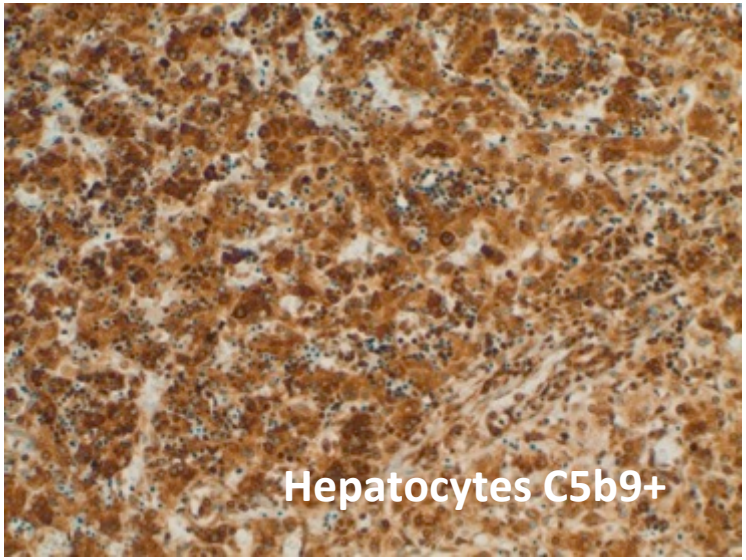
Based on :

- demonstration of extrahepatic siderosis
  - biopsy of oral mucosal salivary glands: Perls staining
  - T2-weighed MRI : low signal intensity in pancreas (heart and adrenal glands) compared to spleen
- Immunohistochemical study with antiC5b9: positive staining on or in hepatocytes >75%

GALD: diagnosis







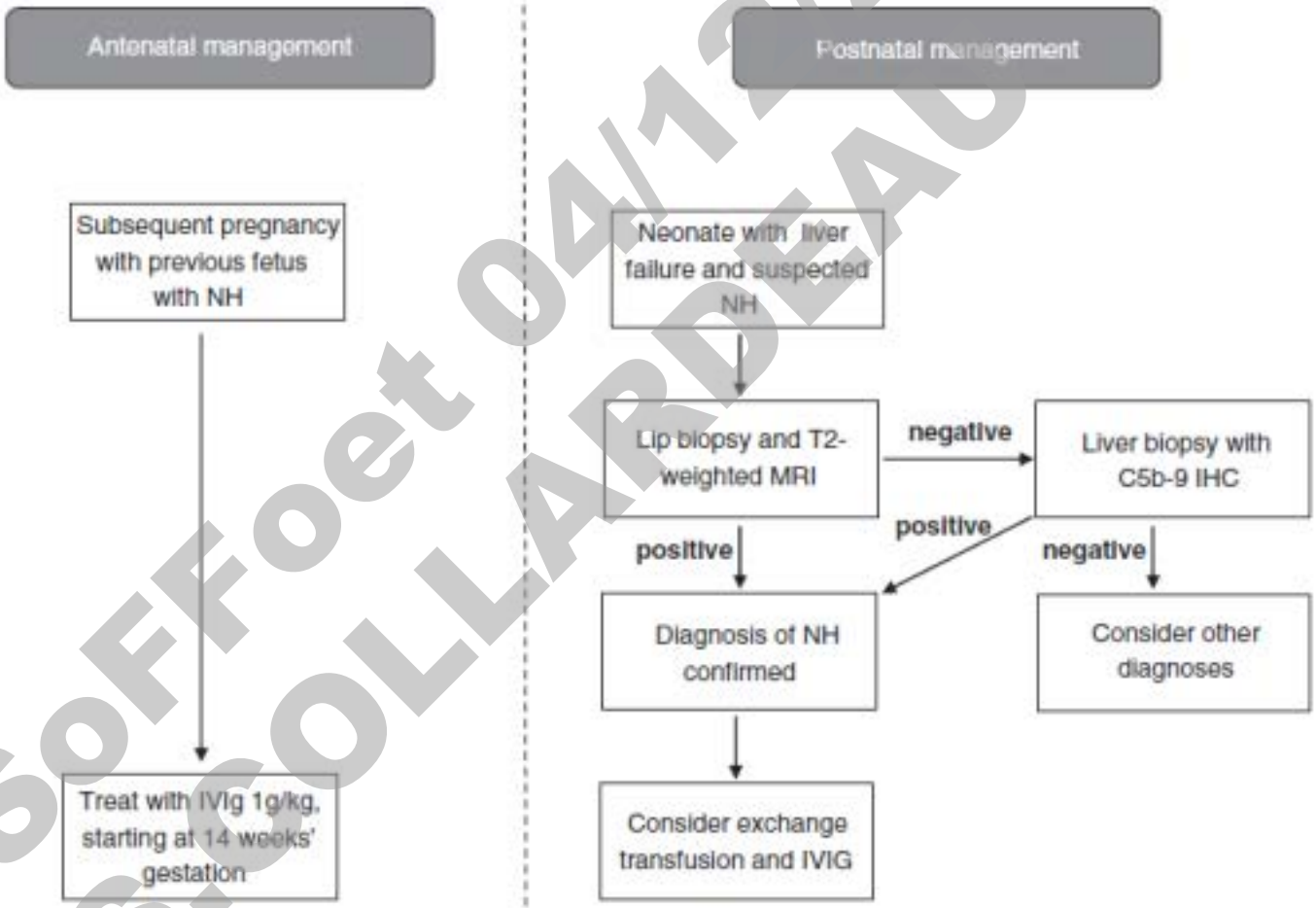
GALD: diagnosis and management

PRENATAL DIAGNOSIS

REVIEW

Neonatal hemochromatosis: management, outcome, and prevention

Enrico Lopriore[1]*, M. Luisa Mearin[1], Dick Oepkes[2], Roland Devlieger[3] and Peter F. Whitington[4]



Problématiques

1/ la surcharge en fer extrahépatique est-elle spécifique et suffisante pour le diagnostic de GALD (HNAI) ?

- Listing de toutes les maladies avec surcharge en fer hépatique
- Présence ou non d'une surcharge extrahépatique
- Caractéristiques de la surcharge en fer hépatique et extrahépatique

travail de thèse de Béatrice Nadaud, DESC de fœtopathologie

2/ l'immuno anti-C5b9 est-elle spécifique et suffisante pour le diagnostic de GALD (HNAI) ?

travail de thèse d'Estelle Dubruc, DESC de fœtopathologie

Enjeux économiques et thérapeutiques du traitement par Ig IV

- coût moyen évalué à > USD 100,000 / France 65000 euros/ grossesse
- effets secondaires


LA FRESQUE
DES LYONNAIS
LE POT BEAUJOLAIS
VACHON
Merci à tous !