Histologic Features of the Liver in Insulin Resistance–Associated Iron Overload

A Study of 139 Patients

Bruno Turlin, MD,[1,2] Michel H. Mendler, MD,[2,3] Romain Moirand, MD, PhD,[2,3] Dominique Guyader, MD, PhD,[2,3] Anne Guillygomarc'h, MD,[2,3] and Yves Deugnier, MD[2,3]

Key Words: Iron overload; Liver; Steatosis; Fibrosis; Genetic hemochromatosis

Abstract

The aim of the present study was to describe histologic features of the liver in insulin resistance–associated hepatic iron overload (IR-HIO), defined as the association of metabolic disorders and hepatic iron overload. We included 139 patients in the study on the basis of one or more metabolic disorders and liver iron overload unrelated to usual causes. Liver biopsy specimens were reviewed, and histologic data were compared with those of a previously published, well-defined population with genetic hemochromatosis.

Iron overload was characterized by a mixed pattern with iron deposits in hepatocytes and sinusoidal cells. Steatosis was present in 59.7% of patients with inflammation in 32.4% of cases. Periportal fibrosis was found in 67.4% of patients. These patients were older, had higher sinusoidal iron scores, and had a higher prevalence of steatosis and inflammation than patients without fibrosis. Iron overload in IR-HIO was histologically different from that in genetic hemochromatosis.

The association between several components of the insulin resistance syndrome (overweight, hyperlipidemia, and abnormal glucose metabolism) and the development of hepatic iron overload has been described.[1-5] Patients with such insulin resistance–associated hepatic iron overload (IR-HIO) usually are middle-aged men with mild to moderate iron excess.[6]

HFE mutations (C282Y and H63D) involved in genetic hemochromatosis (GH)[7] are not responsible for the development of IR-HIO, but compound heterozygosity (ie, heterozygosity for both mutations) may have a role in the overexpression of iron burden.[6] Before the discovery of the *HFE* gene, IR-HIO often was mistaken for early or mild hemochromatosis. In fact IR-HIO is a distinct entity that integrates reports of iron metabolism abnormalities in various conditions such as hyperferritinemia with normal transferrin saturation,[3] steatohepatitis,[2,5,8] and type 2 diabetes.[4]

The aim of the present study was to document in detail the histologic hepatic features of IR-HIO and to compare them with those in well-defined cases of hemochromatosis.

Materials and Methods

Patients

We included 139 patients (age, 29-78; M/F ratio, 119:20) in the study based on the following criteria: (1) one or more of the following metabolic disorders: body mass index (BMI) more than 25 kg/m^2; abnormal glucose metabolism (requirement of antidiabetic therapy or World Health Organization criteria for impaired glucose intolerance or diabetes mellitus[9]); hyperlipidemia (total fasting plasma cholesterol

level >240 mg/dL [>6.2 mmol/L], serum triglycerides level, >150 mg/dL [>1.7 mmol/L], or receiving hypolipemic treatment); and (2) liver iron overload diagnosed by histologic examination (total iron score [TIS] >3) and/or biochemical determination (liver iron concentration [LIC] >36 µmol/g dry weight; reference range, <36 µmol/g dry weight) and unexplained by the usual causes of iron excess: C282Y homozygosity, chronic alcoholism (past or present chronic alcohol use [>60 g/d in men or 40g/d in women] or biochemical features of alcoholism), excess oral intake of iron, repeated blood transfusions, chronic hepatitis according to biochemical data and liver biopsy (hepatitis C and B were excluded by serologic tests in all patients), hematologic disorders (blood cell count), aceruloplasminemia, inflammatory syndrome, or porphyria cutanea tarda (uroporphyrin inclusions on liver biopsy).

Biochemical Methods

Serum tests were performed early in the morning after overnight fasting and included serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, gamma glutamyltranspeptidase (GGT) level, iron level, transferrin saturation, and ferritin level. LIC was determined according to the colorimetric method (reference range, <36 µmol/g dry weight) of Barry and Sherlock.[10] It permitted calculation of the *hepatic iron index*, defined as the LIC/age ratio and expressed as micromoles per gram per year.[11]

Genotype

Testing for *HFE* mutations was performed as described earlier.[12] Allelic frequencies of *HFE* mutations were compared with those of control populations from Brittany.[13]

Pathologic Methods

Five-micrometer-thick, formalin-fixed, paraffin-embedded liver sections were stained with hematoxylin-eosin-saffron, Sirius red, and Perls. Liver biopsy specimens were reviewed by one of us (B.T.) for the assessment of fibrosis, steatosis, inflammation, degenerative hepatocytic changes, and siderosis, without knowledge of clinical background.

Fibrosis was semiquantitatively staged according to the Chevallier system,[14] taking into account fibrosis in the portal tract (PTF, 0-3), central venule (CVF, 0-2), and the Disse space (DSF, 0-2) and the number (NS, 0-3) and size of septa (SS, 0-5), leading to a total fibrosis score (TFS) ranging from 0 to 23 [TFS = PTF + CVF + DSF + 2 × (NS + SS)].

Steatosis was assessed semiquantitatively according to a 5-grade scale (0, absent or present in <5% of hepatocytes; +, ≥5% and <25%; 2+, ≥25% and <50%; 3+, ≥50% and <75%; and 4+, ≥75%) and qualitatively by type (macrovesicular, microvesicular, or mixed) and location (perivenular, periportal, or diffuse).

Portal and lobular inflammation were assessed separately as present (+) or absent (0) and by type (lymphocytic, polymorphonuclear, or mixed). All degenerative changes, including hepatocytic ballooning, acidophilic bodies, cytolytic necrosis, and Mallory bodies were recorded separately as present (+) or absent (0).

Patients were grouped into 1 of 3 classifications according to fatty infiltration: no steatosis, isolated steatosis, or steatosis plus inflammation (steatohepatitis). Steatohepatitis with a pseudoalcoholic pattern, defined by the presence of sinusoidal fibrosis, polymorphonuclear infiltration, and degenerative or necrotic hepatocytic damage irrespective of the presence or absence of Mallory bodies, also was reported.

Iron deposits were assessed semiquantitatively using the method of Deugnier et al,[15] modified according to Turlin and Deugnier.[16] This method separately quantifies iron within hepatocytes, sinusoidal cells (SIS), and connective tissue with correction of the score by a coefficient of heterogeneity (1-2/3-1/3), leading to a TIS ranging from 0 to 60. The sinusoidal iron score/total iron score ratio was calculated for each case.

Statistical Methods

Results are given as median (minimum-maximum) for quantitative data and number (percentage) for qualitative data. The Mann-Whitney, Kruskal-Wallis, chi-square, and Fisher exact tests were used as appropriate. A P value lower than .05 was considered significant.

Values of parameters in patients with IR-HIO were compared with those obtained in a previous pathologic study in patients with GH.[15] Since the present study and the study of patients with GH were performed by some of the same authors using identical methods, and because almost all patients (96.3%) in Brittany, France, diagnosed as having GH on phenotypic criteria have been shown to be homozygous for the C282Y mutation,[17] these 2 populations were considered comparable.

Results

General Characteristics of Patients

Patients were predominantly male (85.6%) and middle-aged (53 years; range, 29-78 years). The most prevalent metabolic disorder was a BMI greater than 25 (107/133 [80.5%]; the BMI was >27 in 67 and >30 in 28 patients), followed by abnormal lipid (71/95 [75%]) or glucose (38/89 [43%]) metabolism. Despite an increased LIC (90 µmol/g dry weight [38-332 µmol/g dry weight]), the serum iron level (140 µg/dL [25 µmol/L]; range, 50-274 µg/dL [9-49

µmol/L]), transferrin saturation (40%; range, 13%-94%), and serum ferritin level (591 ng/mL [591 µg/L]; range, 131-1,920 ng/mL [131-1,920 µg/L]) were normal in 71 (51.1%), 94 (67.6%), and 12 (8.6%) of the cases, respectively. The AST, ALT, and GGT levels were elevated, respectively, in 5.1% (7/136), 12.5% (17/136), and 25% (32/128) of the cases. As expected, allelic frequencies of *HFE* mutations were significantly higher than in the control population (C282Y, 17.4% vs 9.4%; H63D, 32.2% vs 16.9%; $P < .0001$), and the decreased number of patients free of mutations was due only to an increased frequency in compound heterozygosity.

Histologic Data

Histologic data for the 139 patients with IR-HIO are given in **Table 1**.

Iron

Iron overload was most often of mixed pattern (118 cases [84.9%]), consisting of deposits in both hepatocytes and in sinusoidal cells. Parenchymal iron deposits decreased along a gradient from the Rappaport zones 1 to 3. Associated mesenchymal iron deposition was higher than expected according to parenchymal load. In 76 cases (54.7%), iron deposition within periportal hepatocytes was heterogeneous, some cells presenting with marked iron overload while adjacent cells had no or little iron **Image 1**. Mesenchymal deposits were diffusely distributed throughout the hepatic acinus **Image 2**. In a small number of cases, iron was found within portal tracts, usually in macrophages. No significant iron deposition was found in vascular walls or in biliary cells.

Only 21 cases (15.1%) had pure parenchymal and periportal iron overload, 2 of which had associated cirrhosis.

Table 1
Histologic Data for 139 Patients With Insulin Resistance–Associated Iron Overload

Variable	Results
Iron overload scores (possible range)*	
Hepatocytic (0-36)	9 (3-21)
Sinusoidal (0-12)	3 (0-10)
Portal (0-12)	0 (0-4)
Total (0-60)	11 (2-30)
SIS/TIS ratio (%)	25 (0-67)
Steatosis†	83 (60.1)
Inflammation†	
Portal	45 (32.4)
Lobular	80 (57.6)
Hepatocytic changes†	
Ballooning	55 (39.6)
Acidophilic bodies	4 (2.9)
Necrosis	36 (25.9)
Mallory bodies	9 (6.5)
Total fibrosis score (possible range, 0-23)	1 (0-13)

SIS/TIS, sinusoidal iron score/total iron score.
* Data are given as median (minimum-maximum).
† Data are given as number (percentage).

Histologic iron quantification, as well as LIC, demonstrated moderate iron overload, ranging from 3 to 30 and from 38 to 332 µmol/g, respectively. The SIS/TIS ratio was 25% (0%-67%).

Steatosis

Steatosis was present in 83 biopsy specimens (59.7%), of which all were macrovesicular, except in 1 case. Topography was centrilobular **Image 3** in 26 cases (31%), periportal in 1 (1%), and without zonal distribution in 56 (67%). Steatosis was grade I in 65% of cases (54/83), grade II in 19% (16/83), and grade III in 16% (13/83).

Inflammation

Portal and lobular inflammation were present, respectively, in 45 (32.4%) and 80 (57.6%) cases. It was usually lymphocytic (96% [43/45] of portal and 70% [56/80] of lobular cases of inflammation). Prominent polymorphonuclear inflammation was found in 1 case only, but mixed inflammation was seen in 2 cases of portal and 22 cases of lobular inflammation. Portal and lobular inflammation were marked in 5 and 16 cases, respectively.

Degenerative Changes

The most common degenerative hepatocytic change was ballooning, which was found in 55 cases (39.6%). Other features, including necrosis, acidophilic bodies, and Mallory bodies, were less frequent (25.9%, 2.9%, and 6.5% of cases, respectively).

Fibrosis

Only 29 cases (22.0%) were free of fibrosis. The TFS was 1 in 38 cases (28.8%), 2 in 33 cases (25.0%), and higher than 2 in 32 cases (24.2%). Periportal fibrosis was found in 89 cases (67.4%) (nonextensive in 70 and extensive in 19 [6 with and 13 without cirrhosis]). Isolated sinusoidal fibrosis and perivenular fibrosis were present in 9 and 10 cases, respectively.

Summary

As a whole, and without taking into account iron overload, histologic assessment revealed the following: (1) normal liver without steatosis or inflammation in 56 patients (40.3%), (2) isolated steatosis in 40 patients (28.8%), and (3) steatosis plus inflammation (steatohepatitis) in 43 patients (30.9%). Of the 43 patients with steatohepatitis, 16 had the pseudoalcoholic pattern **Image 4**, as described by Ludwig et al.[18]

Correlations

Iron Overload Pattern

Patients with pure parenchymal iron overload (n = 21) were more frequently women and had a lower serum ferritin

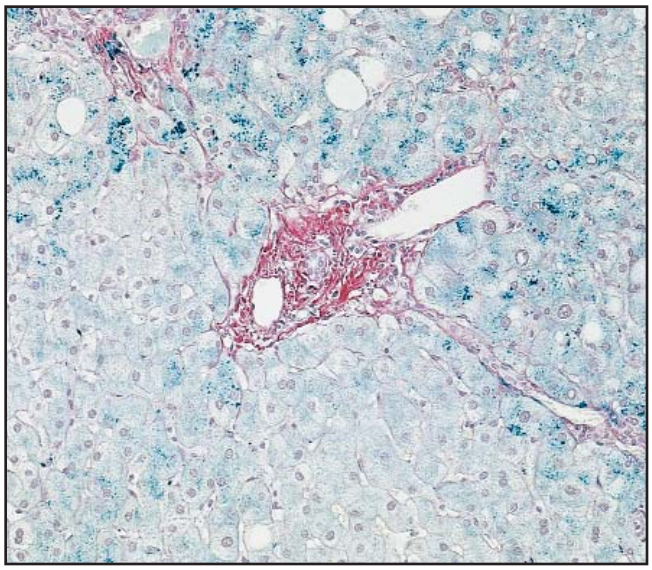

Image 1 Heterogeneous periportal distribution of parenchymal iron overload in a patient with insulin resistance–associated hepatic iron overload. The portal tract is enlarged by nonextensive fibrosis (Sirius red plus Perls, original magnification ×100).

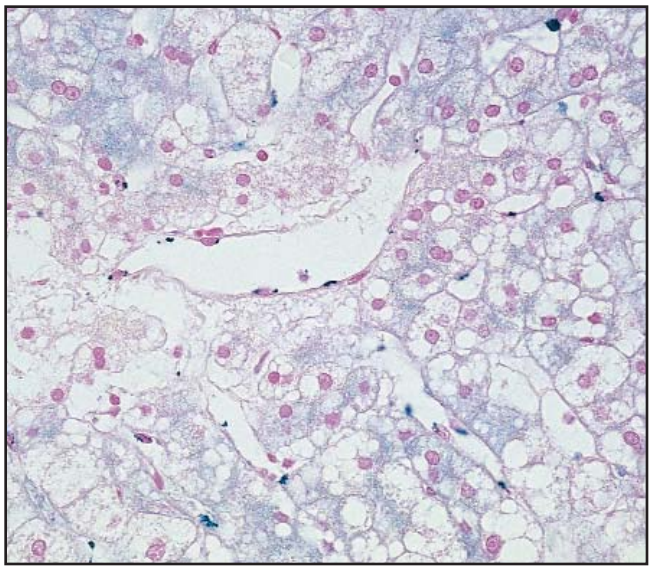

Image 2 Widespread distribution of sinusoidal iron overload throughout the hepatic lobule in contrast with faint parenchymal iron content in a patient with insulin resistance–associated hepatic iron overload (Perls, original magnification ×200).

level, TIS, and periportal fibrosis score than those with mixed iron overload **Table 2**. As a whole, 10 of 21 patients with pure parenchymal iron overload had a normal liver, except for the presence of iron overload.

Steatosis

Compared with patients free of steatosis, patients with steatosis were older and more overweight; had higher serum enzyme and ferritin levels; had higher frequencies of

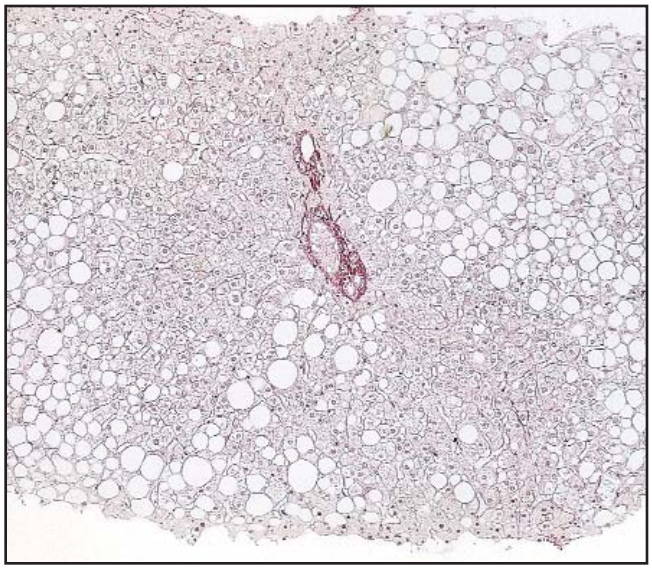

Image 3 Centrilobular macrovesicular steatosis in a patient with insulin resistance–associated hepatic iron overload (Sirius red, original magnification ×100).

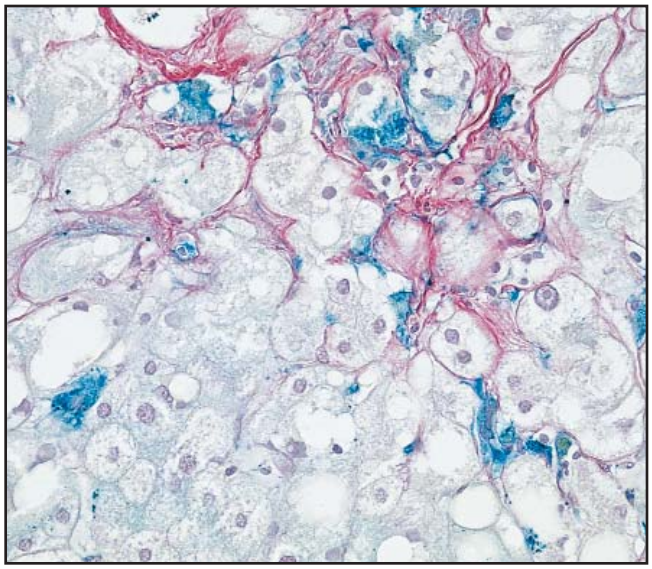

Image 4 Hepatitis foci with fibrosis in centrilobular area in a nonalcoholic patient with insulin resistance–associated hepatic iron overload. Note the marked iron overload in sinusoidal cells (Sirius red plus Perls, original magnification ×200).

Table 2
Clinical, Biochemical, and Histologic Data That Were Significantly Different in Patients With Insulin Resistance–Associated Iron Overload According to Overload Pattern*

	Iron Overload Pattern		
	Pure Parenchymal (n = 21)	Mixed (n = 118)	*P*
Clinical and biochemical data			
No. (%) women	7 (33)	13 (11.0)	<.015
Serum ferritin level (µg/L; reference range, <400)	431 (131-1,314)	650 (163-1,920)	<.0001
Histologic data			
Total iron score (possible range, 0-60)	9 (2-12)	12 (4-30)	<.0001
No. (%) with periportal fibrosis	8 (38)	81 (68.6)	<.01

* Data are given as median (minimum-maximum) unless otherwise indicated.

periportal fibrosis, portal and lobular inflammation, hepatocytic ballooning, and sinusoidal iron; and had a lower frequency of genotype with the C282Y mutation (C282Y heterozygosity plus compound heterozygosity) (48.2% vs 26.5%; $P < .02$) **Table 3**.

Fibrosis

Patients with fibrosis were older and had higher serum ferritin levels, sinusoidal iron scores, prevalence of steatosis, portal inflammation, and ballooning changes than patients without fibrosis **Table 4**. There was a positive but weak correlation between TFS and TIS. By contrast, there was a significant correlation between TFS and SIS ($P = .0011$), which reinforces the link between fibrosis and sinusoidal iron deposition. Periportal fibrosis was associated with SIS, mainly with SIS in zone 1 ($r = 0.211$; $P = .0001$).

Comparison With Patients With GH

Iron overload in patients with IR-HIO was milder compared with that in patients with GH **Table 5**. This difference was not due to age since patients with IR-HIO were older than those with GH ($P < .0001$). The pattern of liver siderosis also was different in patients with IR-HIO, dominated by a mixed pattern of iron deposition, compared with patients with GH who exhibited a parenchymal pattern. This was well demonstrated by the SIS/TIS ratio, which was 25% in patients with IR-HIO and 15% in patients with GH ($P < .0001$). The sinusoidal iron score did not differ

Table 3
Clinical, Biochemical, and Histologic Data That Were Significantly Different in Patients With Insulin Resistance–Associated Iron Overload With or Without Steatosis*

	Steatosis		
	Absent (n = 56)	Present (n = 83)	*P*
Clinical and biochemical data			
Age (y)	50 (29-73)	57 (37-78)	.0081
Body mass index (kg/m^2; reference range, <25)	26 (19-37)	28 (22-39)	.0003
AST (x ULN)	0.4 (0.2-5.3)	0.5 (0.2-1.7)	.0003
ALT (x ULN)	0.4 (0.1-1.3)	0.6 (0.2-2.2)	.0001
GGT (x ULN)	0.7 (0.3-3.7)	1 (0.3-8.4)	.0109
Serum ferritin (µg/L; reference range, <400)	488 (131-1,713)	675 (188-1,920)	.0018
Genotype†			
No mutation	11 (20)	32 (39)	.0180
C282Y heterozygosity	10 (18)	5 (6)	.0274
H63D heterozygosity	15 (27)	24 (29)	NS
H63D homozygosity	3 (5)	5 (6)	NS
Compound heterozygosity	17 (30)	17 (20)	NS
Histologic data			
Sinusoidal iron score (possible range, 0-12)	2.5 (0-8)	4 (0-10)	.0006
SIS/TIS ratio (%)	17 (0-67)	31 (0-62)	.0045
Total fibrosis score (possible range, 0-23)	1 (0-12)	2 (0-13)	<.02
Portal inflammation†	12 (21)	33 (40)	<.03
Lobular inflammation†	21 (38)	59 (71)	.0001
Hepatocytic ballooning†	7 (12)	48 (58)	<.0001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltranspeptidase; NS, not significant; SIS/TIS, sinusoidal iron score/total iron score; ULN, upper limit of normal.
* Data are given as median (minimum-maximum) unless otherwise indicated.
† Data are given as number (percentage).

Table 4
Clinical, Biochemical, and Histologic Data That Were Significantly Different in Patients With Insulin Resistance–Associated Iron Overload With or Without Fibrosis*

	Fibrosis		
	Absent (n = 29)	Present (n = 103)	*P*
Clinical and biochemical data			
Age (y)	46 (34-69)	55 (29-78)	.0025
Serum ferritin (µg/L; reference range, <400)	473 (131-1,590)	611 (163-1,920)	.0155
Histologic data			
Iron overload			
Sinusoidal (possible range, 0-12)	2 (0-7)	3 (0-10)	.0089
SIS/TIS ratio (%)	17 (0-57)	30 (0-67)	.0047
Inflammation†			
Portal	4 (14)	40 (38.8)	.0142
Ballooning	6 (21)	48 (46.6)	.0177
Steatosis	12 (41)	67 (65.0)	.0313

SIS/TIS, sinusoidal iron score/total iron score.
* Data are given as median (minimum-maximum) unless otherwise indicated.
† Data are given as number (percentage).

Table 5
Clinical, Biochemical, and Histologic Data in the Present Series of Patients With IR-HIO Compared With Patients With Hemochromatosis*[15]

	IR-HIO (n = 139)	GH (n = 135)	*P*
Clinical and biochemical data			
Age (y)	53 (29-78)	43 (14-76)	<.0001
Women†	20 (14)	37 (27)	.0122
TS (%; reference range, <45)	40 (13-94)	80 (2-100)	<.0001
Ferritin (µg/L; reference range, <400)	591 (131-1,920)	987 (158-9,237)	<.0001
LIC (µmol/g; reference range, <36)	90 (38-332)	270 (61-854)	<.0001
HII (µmol/g per y)	1.7 (0.5-4.8)	6.7 (1.3-21.6)	<.0001
Histologic data			
Hepatocytic iron score (possible range, 0-36)	9 (3-21)	18 (9-30)	<.0001
Sinusoidal iron score (possible range, 0-12)	3 (0-10)	4 (0-10)	.0830
Portal iron score (possible range, 0-12)	0 (0-4)	3.5 (0-8)	<.0001
Total iron score (possible range, 0-12)	11 (2-30)	25 (9-47)	<.0001
SIS/TIS ratio (%)	25 (0-67)	15 (0-28)	<.0001
SIS Z3 > HIS Z3†	63 (47)	5 (4)	<.0001
Steatosis†	83 (60)	45 (33)	<.0001

GH, genetic hemochromatosis; HII, hepatic iron index; IR-HIO, insulin resistance–associated hepatic iron overload; LIC, liver iron concentration; SIS/TIS, sinusoidal iron score/total iron score; SIS Z3 > HIS Z3, sinusoidal iron score in Rappaport zone 3 higher than hepatocytic iron score in Rappaport zone 3; TS, transferrin saturation.
* Data are given as median (minimum-maximum) unless otherwise indicated.
† Data are given as number (percentage).

significantly between the 2 groups. However, sinusoidal iron deposits were found throughout the whole lobule without zonal predominance in patients with IR-HIO, while they manifested with a decreasing gradient from periportal to centrilobular areas in patients with GH. A sinusoidal iron score in zone 3 greater than the hepatocytic iron score in zone 3 was found in only 5 patients with GH (3.7%), but in 63 patients with IR-HIO (45.3%). In addition, in 56% of patients with IR-HIO, iron content of adjacent periportal hepatocytes was heterogeneous, a feature never found in patients with GH. Patients with GH with fibrosis had a higher LIC than patients with IR-HIO with fibrosis (346 µmol/g [67-854 µmol/g] vs 88 µmol/g [38-332 µmol/g];$P < .0001$).

Steatosis was twice as frequent in patients with IR-HIO compared with patients with GH (60% and 33%, respectively) and often was associated with inflammatory lesions in patients with IR-HIO. No steatohepatitis was reported in patients with GH.[15]

Discussion

In patients with IR-HIO, typical liver pathologic features were mixed iron overload, macrovesicular steatosis, lobular inflammation, and, to a lesser extent, portal inflammation and fibrosis. This pattern was quite different from that previously described in patients with GH,[15] who showed increased iron deposits and less or little steatosis and hepatocytic lesions.

The present data indicate that pathologic features can easily differentiate IR-HIO from GH in most instances. With respect to iron deposits, hepatocytic deposits were located mostly in the periportal area with a heterogeneous pattern from one cell to another (Image 1), and sinusoidal deposits were distributed throughout the lobule (Image 2). This particular iron distribution is well demonstrated by the sinusoidal iron score, which frequently is higher than the hepatocytic iron score in IR-HIO (45.3%) but rarely in GH (3.7%). This contrast between hepatocytic and sinusoidal iron deposition could be considered the hallmark of the syndrome. Indeed, in GH cases, sinusoidal iron content increases parallel to hepatocytic iron content and remains located close to parenchymal iron deposition.[15] However, histologic presentation of iron deposition in the IR-HIO syndrome is nonspecific, as a similar pattern could be seen in other conditions such as chronic hepatitis C infection.

Another important finding of the present study was the demonstration of fibrosis in 67.4% of patients. This underscores the clinical relevance of IR-HIO, since fibrosis is a critical breakpoint for prognosis of liver disease. However, in IR-HIO, the development of fibrosis was observed for a much lower hepatic iron burden than in GH. By showing that increased age and the incidence of steatosis and steatohepatitis were associated with the development of fibrosis, our data suggest that the mechanism of fibrosis is a multifactorial process. This is in accordance with data suggesting the role of iron in the development of fibrosis in patients with nonalcoholic steatohepatitis[5,8] and the effect of steatosis in patients with chronic hepatitis C.[19]

The high correlation between the sinusoidal iron score and the fibrosis score in patients with GH[15] suggests a relationship between sinusoidal iron deposition and the development of fibrosis in IR-HIO. It is interesting to note that again, in the present study, patients with fibrosis had significant sinusoidal iron scores. The high SIS/TIS ratio in IR-HIO might explain the high frequency of fibrosis in such patients. Thus, in IR-HIO, sinusoidal iron, in addition to steatosis and inflammation, could represent the histologic mark of disease activity and progression.

Iron overload in GH is secondary to intestinal iron hyperabsorption. Iron then enters the liver through the portal vein, which explains why iron deposition primarily takes place within periportal hepatocytes. As previously shown,[15] sinusoidal deposits are secondary to iron redistribution from sideronecrotic hepatocytes to macrophages and remain much less abundant than hepatocytic deposits, even in the highly iron-overloaded liver. In IR-HIO, sinusoidal iron deposition is markedly more abundant than that expected from the amount of hepatocytic iron. It is therefore likely that the pathogenetic mechanisms of iron overload are different in GH and IR-HIO. The periportal distribution of hepatocytic iron in IR-HIO may suggest some degree of intestinal iron hyperabsorption, which, however, remains to be proven. Iron deposition within sinusoidal cells of the entire lobule may suggest that sinusoidal iron is related to more diffuse lesions such as inflammation and steatosis. This is supported by data presented in Table 3.

Conclusion

In the presence of liver siderosis, even when mild, the pathologist's role is to describe iron deposits according to their location (cellular and zonal) and intensity. Two peculiar characteristics allow differentiation of IR-HIO from GH: iron overload is heterogeneous from one hepatocyte to another in the periportal area, and sinusoidal iron is distributed throughout the lobule. It is important to recognize IR-HIO, given the following: (1) the high frequency of fibrosis even in cases of limited overload; (2) the presence of a histologic mark of fibrosis (sinusoidal iron); and (3) the ability to easily and inexpensively treat this iron burden (phlebotomy). Understanding the diagnosis of IR-HIO in pathology is relevant when one considers not only its high prevalence[6] but also its possible association with other liver diseases such as hepatitis C,[19] leading to an increased risk of fibrosis development.

From the [1]Laboratory of Pathology B, [2]INSERM U522, and [3]Liver Unit, University Hospital Pontchaillou, Rennes, France.

Address reprint requests to Dr Turlin: Anatomie Pathologique B, Hôpital Pontchaillou, 2 rue H Le Guilloux, 35033 Rennes cedex, France.

Presented as an abstract (oral presentation) during the annual meeting of the Société Française de Pathologie, December 8-10, 1998; Paris, France.

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