Rare Liver Diseases With Near-Normal Histology: A Review Focusing on Metabolic, Storage, and Inclusion Disorders

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Abstract: Despite the growing availability of noninvasive and faster diagnostic modalities, biopsy remains an important tool in the diagnosis and management of liver diseases. However, it is not uncommon that liver biopsies reveal normal or near normal histologic findings in patients with abnormal liver biochemistries, elevated autoantibodies, clinical findings suggestive of portal hypertension, systemic autoimmune or inflammatory diseases, hepatomegaly, cirrhosis by imaging, or other indications. These scenarios present significant diagnostic challenges and are rarely discussed in detail in the literature or textbooks. This article aims to provide a comprehensive review of a group of selected rare liver diseases, with a focus on metabolic, storage and inclusion disorders, that may exhibit a near-normal histology on biopsy. By recognizing subtle histologic features and correlating with clinical history, laboratory results and imaging findings, it is often possible to narrow down the differential diagnosis. In many cases, this integrative approach can yield a definitive diagnosis, allowing for tailored treatment and better patient outcomes.

Key Words: rare liver diseases, liver biopsy, normal histology, near-normal histology, metabolic disorder, storage disorder, inclusion

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Liver biopsy remains the gold standard and definitive diagnostic tool for investigating various abnormal liver conditions, evaluating prognosis and assessing treatment response, despite the emergence of noninvasive and/or faster diagnostic modalities. It is indicated in clinical settings ranging from abnormal liver function tests, unknown etiology of liver injury, unusual clinical presentations of known liver diseases, screening for metabolic liver disorders, evaluating liver involvement in systemic diseases, staging underlying liver disease, assessing treatment effects, liver allograft evaluation, to mass lesion diagnosis. It has been reported that biopsy can help identify the cause of liver disease in 84% of patients with abnormal liver function tests.[1]

However, studies have found up to 10% of liver biopsies to be normal or near-normal.[2] This can be frustrating to pathologists and treating physicians because the biopsies may be performed as the last resort to help explain abnormal liver biochemistries, elevated autoimmune antibodies, clinical findings suggestive of portal hypertension, potential hepatic involvement by systemic diseases, hepatomegaly, cirrhosis by imaging, or other indications. In some cases, the discordance may be caused by the lack of specificity of laboratory or imaging tests, irregular distribution of parenchymal disease in the liver (sampling error), or temporal fluctuations of disease activity.[2] While some patients will show normalized liver tests and no evidence of liver disease during follow-up, others may eventually develop chronic liver diseases such as autoimmune and steatotic liver diseases.[3,4]

Liver biopsies that are near-normal may exhibit a spectrum of nonspecific histologic findings. In general, the normal hepatic architecture is well preserved and there is no significant fibrosis. Portal tracts may contain sparse inflammatory cell infiltrates, but bile ducts and portal vasculature are usually unremarkable. The lobules may show scattered inflammatory cells, single or rare granulomas, rare acidophil bodies, minimal steatosis, occasional glycogenated nuclei, hepatocyte anisonucleosis, mild sinusoidal dilatation, and minimal to mild iron deposition. In contrast, some seemly normal or near-normal biopsies may harbor subtle but important changes that are crucial to the diagnosis of liver diseases. Examples may include hemophagocytic lymphohistiocytosis (hemophagocytic syndrome) (Fig. 1A), nodular regenerative hyperplasia, obliterative portal venopathy, vanishing bile duct syndrome, Alagille syndrome, cystic fibrosis, and porphyrin metabolism disorders. Bland (pure) cholestasis is another example characterized by predominantly zone 3 canalicular cholestasis without significant lobular or portal inflammation, bile duct injury or features of biliary obstruction (Fig. 1B). Drugs are the most common etiologies of bland cholestasis, with anabolic steroids, oral contraceptives, and antimicrobials being the common culprits.[5] The biopsies may also show scattered or clusters of ceroid-laden macrophages in the lobules and portal tracts, suggesting a resolving phase of lobular injury or bile duct injury such as that caused by transient drug hepatotoxicity and viral hepatitis. This finding is best appreciated on periodic acid-Schiff stain with diastase (PASD) (Fig. 1C).

Generating a clinically meaningful diagnosis or differential diagnosis is challenging when a normal or near-normal biopsy is encountered. It requires adequate medical knowledge, careful histologic assessment, and good clinical correlation. There have been limited discussion and guidance in the literature and textbooks on how to approach such liver biopsies in daily practice.[6] The aim of this article is to provide a comprehensive review of a group of selected uncommon metabolic, storage, and inclusion disorders that may look near-normal on liver biopsies.

WILSON DISEASE

Wilson disease (WD) is an autosomal recessive disorder characterized by impaired copper metabolism due to mutations in the *ATP7B* gene located on chromosome 13q14.3. This gene encodes an ATPase, which incorporates copper into nascent ceruloplasmin and facilitates biliary

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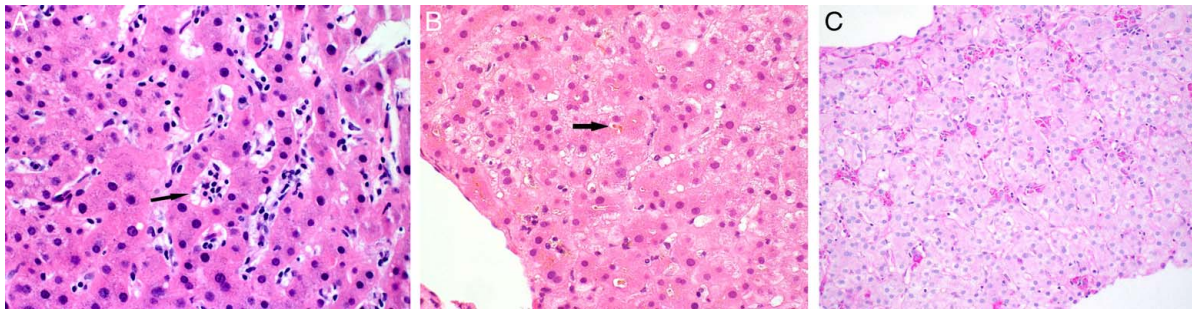

FIGURE 1. A, Hemophagocytic lymphohistiocytosis showing prominent Kupffer cells with engulfed lymphocytes (arrow; origin magnification ×400). B, Bland cholestasis showing canalicular cholestasis (arrow) mainly at centrilobular region (origin magnification ×400). The patient has been taking piperacillin/tazobactam. C, Resolving liver injury showing scattered ceroid-laden macrophages in the lobules (PASD stain, original magnification ×200). These cells are also present in portal tracts.

excretion of copper. Mutations in this gene lead to toxic copper accumulation in various organs, particularly the liver, brain, cornea, and kidneys, and a low serum ceruloplasmin level. Patients with WD present with a wide spectrum of hepatic, neurological, psychiatric, and ophthalmologic manifestations, typically between the ages of 3 and 35 years.[7] The presence of Kayser-Fleischer rings, golden-brown copper deposits in the Descemet's membrane of the cornea, is the characteristic ophthalmologic presentation.

Approximately 42% of WD patients present with hepatic symptoms and signs as the initial clinical manifestation,[8] such as fatigue, abdominal pain, jaundice, ascites, encephalopathy, and coagulopathy. Routine workup may include serum ceruloplasmin, 24-hour urinary copper, serum free copper (nonceruloplasmin-bound copper), and Kayser-Fleischer rings. Identifying *ATP7B* mutations can aid in the diagnosis. To date, ~900 mutations have been identified in this gene,[9–11] but only a minority are known to be pathogenic. In addition, majority of WD patients are compound heterozygotes, while some mutations may occur in the promoter region. A liver biopsy may be the initial workup for abnormal liver tests, with or without clinical suspicion of WD. Therefore, WD should always be included in the differentials in patients with liver disease of unknown etiology, particularly in those aged 5 to 50 years. It should be noted that serum ceruloplasmin is not a reliable marker for WD because it is an acute phase reactant. Its levels can be high in the setting of inflammation, infection, pregnancy, heart disease, leukemia/lymphoma, and certain medications. Individuals with WD may have normal or near-normal ceruloplasmin levels if they develop these conditions. In contrast, its level can be low in other liver diseases with impaired synthetic function and diseases that cause malnutrition, protein loss, and copper deficiency.[11,12]

The liver pathology of WD is highly variable, ranging from minimal or no histologic abnormality, chronic hepatitis, steatosis or steatohepatitis, acute hepatitis or acute liver failure, to cirrhosis.[9,13] Fanni et al[9] examined 127 liver biopsies from 43 WD patients between 1980 and 2018, and found that steatosis was the most common finding, seen in 80% of biopsies. The majority (58%) of these cases showed mixed microvesicular and macrovesicular steatosis, while one-third showed macrovesicular and 9% showed microvesicular steatosis. Steatosis involved all zones in 54% of biopsies and was mainly periportal in 46%. Glycogenated nuclei were found in 71% of cases, frequently in the periportal areas. Ballooned hepatocytes were present in 68% of biopsies in periportal zones and absent in centrilobular areas. Varying degrees of portal and lobular inflammation was identified in 84% of biopsies. Other findings included Mallory-Denk bodies (23%), regenerative nuclear changes (32%), ductular reaction (28%), ground glass cytoplasm (8%), and lipogranulomas (35%). In the 112 biopsies that were evaluable for fibrosis, perivenular, periportal, and bridging fibrosis was detected in 4%, 37%, and 57% of cases. Cirrhosis was seen in 2 biopsies. Only one biopsy showed no fibrosis.

Therefore, the diagnosis of WD requires a high index of suspicion given the variable and nonspecific laboratory and histologic findings. The paraffin block of liver biopsy can be sent for copper quantification. A copper content >250 μg/g dried tissue is essentially diagnostic of WD with a sensitivity of 83%.[14] A value lower than 250 μg/g but higher than normal reference (<50 μg/g) is usually seen in cholestatic liver diseases or heterozygous carriers of WD. Special stains for copper, such as Timm, rhodamine or orcein stains, have limited diagnostic value because of low sensitivity and low specificity.[8,15] A negative staining does not rule out WD. In recent studies, metallothionein (MTH), a cytosolic copper-binding protein in the hepatocytes, was discovered as a potentially powerful diagnostic marker. A large cohort study reported that MTH immunostain was sensitive to all stages of disease and variety of injury patterns on both biopsies and resections, with a sensitivity up to 91.2% by using a threshold of 50% of hepatocytes with at least moderate intensity. In cases with no advanced fibrosis, the sensitivity was 100%.[16,17] Another study also showed similar data of MTH immunostain with an overall sensitivity of 85.7%, specificity of 96.9%, and accuracy of 94.9%.[18] However, zinc treatment can cause false-positive on MTH immunostain.

Figure 2A shows a liver biopsy from a 51-year-old woman with seizure disorder. She was found to have copper deficiency with a plasma copper level of 13.6 μg/dL (normal: 80 to 155 μg/dL). Workup showed a serum ceruloplasmin level of <3 mg/dL (normal: 14 to 45 mg/dL), 24-hour urine copper of 206.5 μg/day (normal: 3 to 45 μg/day), and normal liver biochemistries. The liver biopsy showed essentially normal histology. The biopsy was sent for copper quantification with a result of 1090 μg/g dry weight. The patient was tested for a Copper Metabolism Disorder Panel, a genetic testing for 10 genes related to copper metabolism disorders, including *ATP7B* and the *CP* gene (for aceruloplasminemia). The testing came back negative. She had no

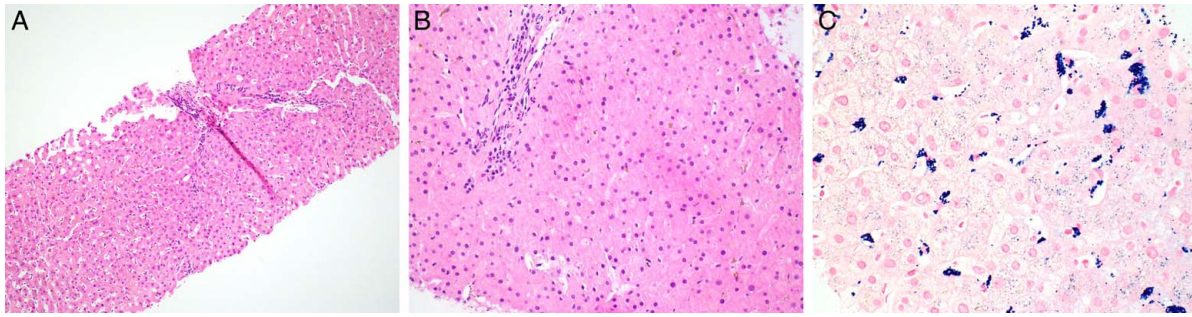

FIGURE 2. A, A liver biopsy from a patient with Wilson disease showing near-normal histology (original magnification ×100). Only minimal nonspecific sinusoidal dilatation is noted. B, A liver biopsy from a patient with chronic kidney disease showing near-normal histology (original magnification ×200). C, Iron stain showing moderate iron deposition in Kupffer cells and mild deposition in hepatocytes (original magnification ×400). Please see this image in color online.

Kayser-Fleischer rings. There was no support for aceruloplasminemia as her iron studies were normal and her liver biopsy showed no iron overload.[19] Given her low serum ceruloplasmin and high urine copper levels, as well as high copper concentration in the liver, WD was diagnosed clinically despite normal liver histology and negative testing for the Copper Metabolism Disorder Panel.

IRON OVERLOAD

Hepatic iron overload results from inherited disorders or acquired conditions. Inherited forms, termed hereditary hemochromatosis (or simply hemochromatosis), are linked to mutations in key genes, including *HFE*, *hemojuvelin (HJV)*, *hepcidin (HAMP)*, *transferrin receptor 2 (TFR2)*, and *ferroportin 1 (FPN/SLC40A1)*.[20] Other rare inherited disorders include ferroportin disease, aceruloplasminemia, atransferrinemia, DMT1 deficiency, and other conditions.[21] Acquired forms, usually termed hemosiderosis, encompass a range of conditions linked to excessive iron supply, systemic diseases, or chronic liver diseases. Although liver biopsy is not necessary for the diagnosis[22] due to easy access to magnetic resonance imaging, laboratory testing for transferrin saturation and ferritin, and genotyping, it remains as a useful tool for early diagnosis, fibrosis assessment, associated lesions, and other underlying conditions.[23] Even in patients with homozygous C282Y, symptoms, and manifestations are extremely variable due to the clinical penetrance observed.[24,25] Biopsy can confirm the amount of iron accumulation in the liver.

While patients with iron overload may be asymptomatic, liver biopsy may reveal findings ranging from minimal iron deposition to advanced cirrhosis. Histologic patterns of iron deposition can be categorized based on distribution, primarily within hepatocytes (parenchymal) or Kupffer cells (reticuloendothelial). Inherited iron overload typically manifests as iron deposition in hepatocytes, particularly in the pericanalicular region. This deposition initially affects zone 1 hepatocytes, with a decreasing gradient of accumulation toward zone 3. Eventually, all zones are similarly involved, and iron may also deposit in duct epithelium, Kupffer cells, and endothelium. Scheuer et al[26] introduced the first semiquantitative scoring schema for hepatocellular iron, which has been widely utilized. This schema uses a simple 1 to 4 scale to grade the severity of iron deposition on Perls Prussian blue staining. Grade 1 represents minimal iron deposition, grade 4 massive iron deposition across all zones without a gradient, and grades 2 and 3 intermediate. For cases without a documented history of hemochromatosis, we send paraffin block for iron quantification if iron stain shows grade 3 or grade 4 iron overload in hepatocytes. A hepatic iron index > 1.9 is highly suggestive of homozygous hemochromatosis, although transfusion-related heavy iron overload is also a possibility. Genetic testing and additional clinical history are helpful to confirm the diagnosis in these cases. An index between 1.0 and 1.9 (normal reference < 1.0) may suggest heterozygous hemochromatosis or nonspecific iron accumulation such as that seen in the setting of alcoholic liver disease.

In contrast, iron accumulation within Kupffer cells and portal macrophages is characteristic of secondary iron overload. An exception is type 4 inherited ferroportin disease, where this pattern may also occur.[27,28] The severity of Kupffer cell iron deposition is generally graded as mild, moderate, or severe (marked); no universally accepted grading system currently exists.[29]

The distribution patterns of iron deposition, whether confined to hepatocytes, Kupffer cells, or exhibiting specific lobular gradients, can provide crucial insights into the underlying etiology. However, mixed patterns are sometimes observed, with iron present in both hepatocytes and Kupffer cells, suggesting multifactorial causes or severe, extensive iron loading.

Excessive iron is potentially hepatotoxic due to oxidative stress.[30] Deugnier and colleagues reported portal, sinusoidal, and septal fibrosis in 63% of liver biopsies from patients with hemochromatosis, and iron-related hepatocyte necrosis (sideronecrosis) in 37% of their cases. The latter is characterized by scattered acidophilic bodies that are often localized mainly in zone 1, in proximity to iron-loaded macrophages and mild lobular inflammation.[22] Mild to moderate portal and periportal lymphohistiocytic inflammation and hepatocyte ballooning were also observed in some cases in this study.[22] Cirrhosis is particularly prevalent in cases with concurrent chronic liver diseases, such as alcoholic liver disease or hepatitis C.[31,32]

Figure 2B illustrates a transjugular liver biopsy from a 69-year-old woman with end-stage renal disease secondary to diabetic glomerulosclerosis. During evaluation for kidney transplantation, abdominal ultrasound revealed hepatomegaly with increased and coarsened echotexture. The biopsy was largely unremarkable except for moderate iron deposition in Kupffer cells and mild deposition in hepatocytes (Fig. 2C). Iatrogenic iron overload is a common finding in

patients with chronic kidney disease undergoing dialysis. This condition is primarily attributed to chronic hemolysis, repeated blood transfusions, and iron supplementation.[33] In these patients, iron deposition predominantly occurs in Kupffer cells.

α1-ANTITRYPSIN DEFICIENCY

α1-Antitrypsin deficiency (AATD) is an autosomal codominant disorder caused by point mutations in the *SERPINA1* gene, which encodes the protease inhibitor (Pi) α1-antitrypsin (A1AT). This protein exhibits broad antiproteolytic and anti-inflammatory functions. A1AT is primarily synthesized in the liver and secreted into the bloodstream. Mutations in the *SERPINA1* gene result in the production of misfolded proteins that accumulate in the endoplasmic reticulum (ER) of hepatocytes, leading to liver injury.[34]

More than 100 alleles/variants have been identified,[35] with some associated with liver disease. The wild-type protein is designated as M, and homozygotes for the wild-type allele are characterized by the PiM phenotype (genotype PiMM). The most common severe deficiency variants are Z and S. Heterozygous PiMS and PiMZ phenotypes do not generally cause disease, but are a risk factor that requires a "second hit" to cause chronic liver disease.[36] In contrast, PiZZ homozygosity results in severe AATD, with ~85% reduction in secreted protein levels,[37] often progressing to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) over time. Phenotypes such as PiSS and PiSZ are associated with milder forms of the disorder compared with PiZZ.

Patients with AATD display highly variable clinical symptoms and disease severity, which depend on age and deficient variants.[38,39] In infants and children, clinical manifestations range from no symptoms to cholestatic liver disease, hepatitis, or progression to cirrhosis, with rare cases of fulminant hepatic failure. Adult patients may similarly exhibit a spectrum of presentations, including asymptomatic state, steatosis, hepatitis, fibrosis, and HCC.

A characteristic histologic feature of AATD is the presence of variably sized, PAS-positive, diastase-resistant eosinophilic globules in periportal hepatocytes. With disease progression, these globules may extend to other zones of the hepatic lobules, and even be distributed diffusely within the lobules. Early-stage diagnosis can be challenging particularly in pediatric patients. In infants younger than 3 months, these diagnostic globules are often subtle or entirely absent, necessitating reliance on phenotyping or genotyping for confirmation.[40] It is critical to distinguish AATD-related cholestasis from other causes, such as neonatal hepatitis or biliary atresia, especially when considering the Kasai procedure for suspected biliary atresia.

Other biopsy findings may include minimal to mild lymphocytic inflammation in portal tracts and lobules, mild hepatocyte anisocytosis, mild steatosis, and variable degrees of fibrosis. Neonatal cases may also show hepatocyte ballooning, giant cell transformation, necrosis, cholestasis, ductopenia, and ductular reaction, mimicking neonatal hepatitis or biliary atresia as mentioned above.

Figure 3 presents a 22-year-old man with Crohn disease treated with solumedrol, infliximab, and methotrexate. He presented with mildly elevated liver enzymes. Autoimmune and hepatitis viral serologies were negative, and ultrasound revealed hepatic steatosis. A liver biopsy was performed to rule out drug-induced liver injury, primary sclerosing cholangitis, and fatty liver disease. Histologic examination of the biopsy revealed minimal to mild lymphocytic infiltrates in portal tracts (Fig. 3A) and vague eosinophilic globules in hepatocytes (Fig. 3B) but otherwise unremarkable. PASD stain demonstrated numerous variably sized hyaline globules in periportal hepatocytes (Fig. 3C), which were further confirmed by immunohistochemistry (IHC) to be A1AT (Fig. 3D). The patient was subsequently found to have a heterozygous A1AT phenotype (PiMZ), with a serum A1AT level of 75 mg/dL (normal: 90 to 200 mg/dL).

It should be mentioned that PASD-positive globules may be incidentally observed in other types of liver diseases in patients without AATD. The globules can even be immunoreactive to anti-A1AT antibodies. Examples include venous outflow impairment secondary to heart failure and Budd-Chiari syndrome,[41] and end-stage liver disease caused by viral hepatitis or alcohol.[42] The globules may show a random distribution and their presence in those conditions bears no clinical implications. Nonetheless, it is important to alert the clinician for the possibility of unexpected AATD even in the presence of an apparent cause of liver disease.

FIBRINOGEN STORAGE DISEASE

Fibrinogen storage disease is caused by abnormal synthesis, accumulation, or secretion of fibrinogen within the hepatic ER. This results in absent or low levels of plasma fibrinogen or the production of dysfunctional fibrinogen, leading to bleeding diathesis. Fibrinogen is primarily synthesized in hepatocytes and comprises three polypeptide chains: α, β, and γ, encoded by the *FGA*, *FGB*, and *FGG* genes, respectively.[43] Mutations in one of these genes (mostly *FGA*) lead to congenital fibrinogen deficiency, which is broadly classified into type I (quantitative) and type II (qualitative).[44,45] Type I deficiency includes afibrinogenemia and hypofibrinogenemia, while type II encompasses dysfibrinogenemia and hypodysfibrinogenemia. Fibrinogen storage can also result from secondary causes, such as acquired defects in protein secretion, typically induced by drugs or infections.[46] Fibrinogen inclusions within hepatocytes have been categorized into 3 types based on histologic and ultrastructural characteristics:[46,47]

- Type I inclusions: polygonal with irregular outlines. Electron microscopy (EM) shows dilated rough ER cisternae packed with tubular structures arranged in fingerprint-like curved bundles.
- Type II inclusions: ground glass appearance. EM shows granular or fibrillar material filling dilated ER cisternae.
- Type III inclusions: round eosinophilic globules surrounded by a clear halo. EM shows similar features to type I or type II inclusions, consisting of tubular or granular material.

Zen and Nishigami[48] proposed to use a less specific term, such as "pale body," for type II and type III inclusions after reevaluating three cases without hypofibrinogenemia. Their findings suggest that type II and type III inclusions are more likely to represent a cellular response to stress rather than mutation-associated inherited fibrinogen storage disorder.[47,48]

Fibrinogen inclusions can be difficult to recognize on H&E stain. The cytoplasmic changes could be misinterpreted as tissue fixation artifact. They are easier to recognize on PASD and phosphotungstic acid-hematoxylin stains. IHC is also useful, but the antibody may not be readily

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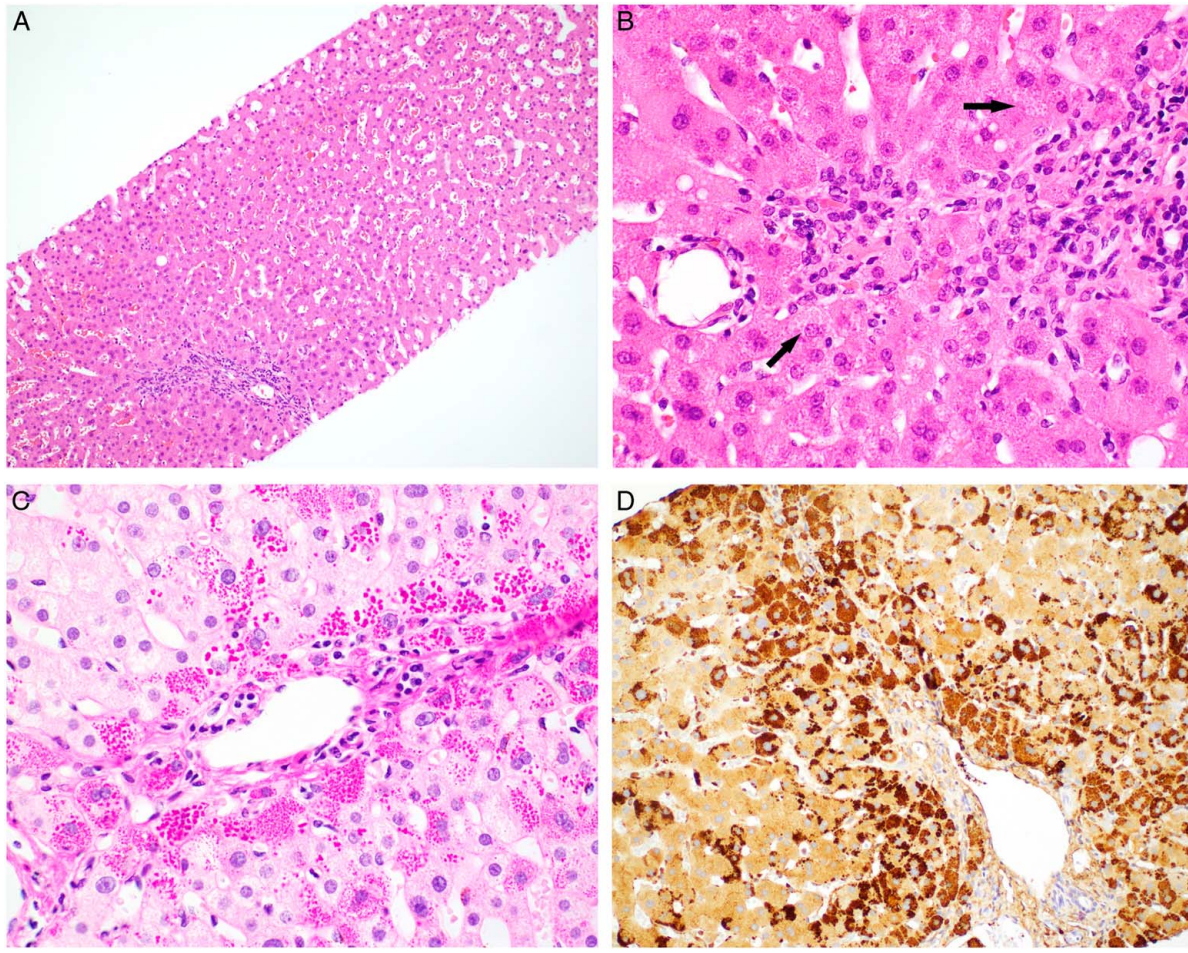

FIGURE 3. A, A liver biopsy from a patient with heterozygous A1AT phenotype (PiMZ) showing near-normal histology (original magnification ×100). Only minimal to mild portal lymphocytic infiltrates and mild sinusoidal dilatation are noted. B, Higher power view showing vague cytoplasmic eosinophilic globules in the periportal hepatocytes (arrows; original magnification ×400). C, PASD stain performed on the same biopsy revealing numerous hyaline globules in periportal hepatocytes (original magnification ×400). D, The cytoplasmic globules in the same biopsy are positive for 1-antitrypsin on IHC (original magnification ×200). Please see this image in color online.

available in most clinical IHC laboratories. The characteristic fingerprint-like EM finding is essentially diagnostic.

Figure 4 presents a 9-year-old boy with mildly elevated liver enzymes, mildly enlarged liver and minor bruises over the shins, discovered during a preoperative evaluation for the excision of a benign skin cyst. Serologic studies were negative for viral infections and autoimmune disorders. Liver biopsy revealed no portal or lobular inflammation,

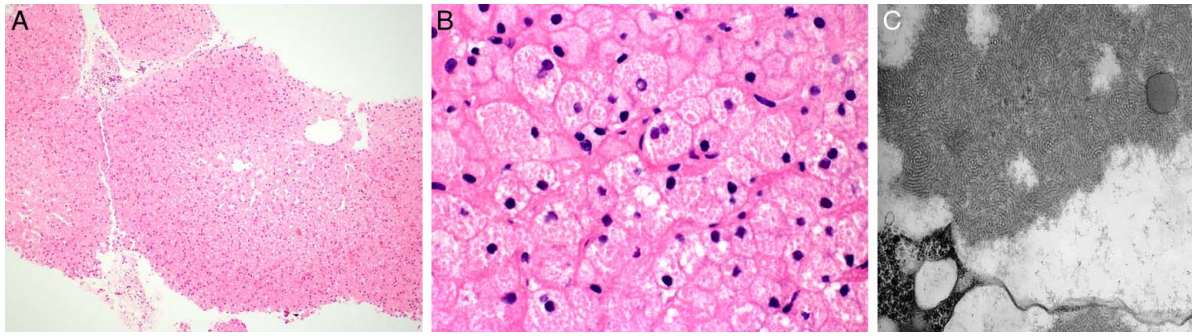

FIGURE 4. A, A liver biopsy from a patient with hypofibrinogenemia showing near-normal histology (original magnification x100). B, High-power view showing enlarged hepatocytes containing numerous vague globular eosinophilic inclusions (original magnification ×600). C, EM examination showing dilated cisternae of the rough endoplasmic reticulum containing densely packed curved tubular electron-dense structures arranged in a fingerprint-like pattern (original magnification ×32,000). Please see this image in color online.

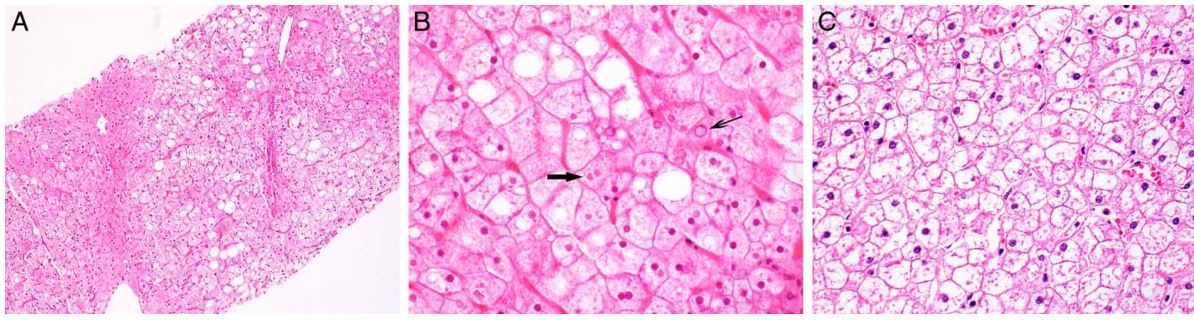

FIGURE 5. A, A liver biopsy from a patient with type 1 diabetes mellitus showing diffuse hepatocyte swelling with pale cytoplasm (original magnification ×100). There is only focal minimal steatosis. B, High power showing abundant pale cytoplasm and thickened cell membranes (original magnification ×400). Megamitochondria (thick arrow) and glycogenated nuclei (thin arrow) are evident. C, A representative section of nonneoplastic liver explanted from a young patient with glycogen storage disease type 1b and hepatocellular adenomatosis (original magnification ×400). Note enlarged and pale hepatocytes with thickened cell membranes.

steatosis, cholestasis, or fibrosis (Fig. 4A). However, hepatocytes exhibited abundant cytoplasm containing multiple vague eosinophilic globular inclusions (Fig. 4B). EM demonstrated dilated cisternae of the rough ER filled with densely packed, curved tubular electron-dense structures arranged in a fingerprint-like pattern (Fig. 4C). Whole exome sequencing identified a heterozygous missense mutation at codon 35 of the *FGA* gene. The patient was diagnosed with hypofibrinogenemia. His plasma fibrinogen level was found to be 85 mg/mL (normal: 215 to 464).

GLYCOGENIC HEPATOPATHY

Glycogenic hepatopathy is most commonly observed in patients with poorly controlled type 1 diabetes mellitus, and less commonly, in those with type 2 diabetes mellitus, dumping syndrome following gastrectomy, anorexia nervosa, and in those on various medications such as high-dose corticosteroids and azathioprine.[49–51] The term was coined in 2006 to emphasize its association with glycogen accumulation, hepatomegaly, and/or elevated liver enzymes.[52] The histologic hallmark is cytoplasmic glycogen accumulation characterized by diffuse hepatocyte swelling with abundant pale cytoplasm and prominent cell borders (Fig. 5A). The swollen hepatocytes often compress adjacent sinusoids. Glycogenated nuclei are a common finding, and giant mitochondria (megamitochondria) may be seen (Fig. 5B). There is usually no significant portal or lobular inflammation, steatosis, or fibrosis, but mild steatosis and mild fibrosis can be seen in a small subset of cases.[49] The prognosis is excellent with improved glycemic control, but relapse can occur.

The above histologic findings are similar to those seen in inherited glycogen storage diseases, particularly types I, III, VI, and IX, which involve the liver[53] (Fig. 5C). However, significant fibrosis with progression to cirrhosis, hepatocellular adenoma, and HCC can occur in patients with inherited glycogen storage diseases.[54]

GLYCOGEN PSEUDO-GROUND GLASS CHANGE

The term "ground glass" is traditionally used to describe hepatocytes containing hepatitis B virus (HBV) surface antigens in the ER[55,56] (Fig. 6A). The term "pseudo-ground glass change" refers to a similar morphology but unrelated to HBV infection.[57] It is characterized by a single, large, distinctive, amphophilic to slightly eosinophilic inclusion-like structure in the cytoplasm of hepatocytes, often surrounded by a thin rim of normal cytoplasm or clear space, and often pushing nuclei to the periphery of the cells (Fig. 6B). These inclusions are positive with PAS staining and sensitive to digestion by diastase, indicating accumulation of glycogen (Fig. 6C). Since they appear as inclusions, they are also called pseudo-ground glass inclusions or pseudoground glass bodies.[58] The inclusions are morphologically similar to those seen in polyglucosan body diseases such as type IV glycogen storage disease and Lafora disease.[59]

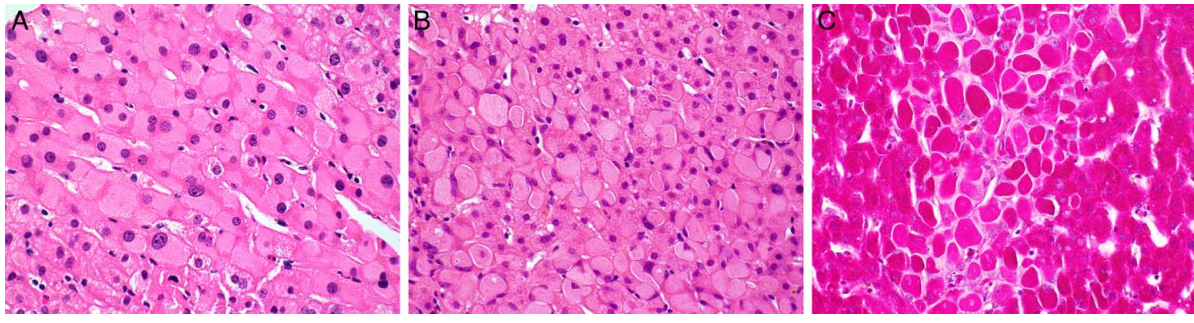

FIGURE 6. A, A biopsy from a patient with chronic hepatitis B showing ground glass hepatocytes (original magnification ×400). This can be confirmed by IHC for hepatitis B viral surface antigen. B, A biopsy from a liver allograft showing pseudo-ground glass change characterized by large and distinctive inclusion bodies in the cytoplasm of hepatocytes (original magnification ×400). C, The inclusion bodies stain positive with PAS and are diastase sensitive (original magnification ×400). Please see this image in color online.

According to a study of 12 cases by Wisell et al,[57] the glycogen pseudo-ground glass change is commonly observed in immunosuppressed individuals receiving multiple medications (polypharmacy), most frequently antibiotics and/or antiseizure drugs. Other drugs linked to pseudo-ground glass change include phenytoin, barbiturates, chlorpromazine, azathioprine, rifampin, and cyanamide (used for alcohol aversion therapy).[60–63] Similar change has also been observed in transplant patients.[63,64] This histologic finding typically occurs in a background of mild inflammation with no or minimal fibrosis. While it can persist for years, it may also resolve over a short period of time. It likely represents cellular adaptation or mild hepatocellular injury, as most cases are associated with only mildly elevated transaminases.

HEPATIC AMYLOIDOSIS

Amyloidosis is a systemic disease resulting from abnormal protein metabolism leading to tissue deposition of misfolded proteins. The reported prevalence of hepatic involvement ranges from 9% to 90% in different studies.[65,66] The clinical presentation of hepatic amyloidosis varies widely, ranging from asymptomatic to severe dysfunction, requiring liver transplantation. Liver biopsy is seldom performed in patients with a known clinical diagnosis of amyloidosis due to the high risk of bleeding. Instead, it is often an incidental and unexpected finding when a biopsy is performed for unexplained liver tests or other unrelated indications. The reported prevalence is 0.4% among patients undergoing liver biopsy.[67]

Amyloid is classified according to its precursor proteins, of which more than 36 types have been identified.[68] The common types of hepatic amyloidosis include those derived from immunoglobulin light chain (AL), serum amyloid A (AA), apolipoprotein A1 (APO), transthyretin (TTR), fibrinogen α (FIB), and leukocyte chemotactic factor-2 (ALECT2). Three histologic patterns of amyloid deposition have been described in the liver.[66,69,70] Subtle cases can be easily overlooked:

- Sinusoidal linear pattern (Fig. 7A): the most common pattern characterized by amyloid material filling the space of Disse, leading to sinusoidal obliteration, hepatocyte atrophy, and eventually hepatocyte extinction.
- Vascular linear pattern (Figs. 7B, C): amyloid deposition within the walls of arteries and veins, as well as within the portal stroma.
- Globular pattern (Figs. 7D, E): discrete globular deposits in the space of Disse, portal tracts, hepatocytes, and Kupffer cells.

AL is the most common type of hepatic amyloidosis followed by TTR.[71] AL and AA typically demonstrate sinusoidal and vascular patterns, while TTR, APO, and FIB show almost exclusively vascular deposition.[66,69] ALECT2 is the only type that exhibits a prominent globular pattern with an extracellular and intracellular distribution.[66,72] However, typing amyloidosis solely based on deposition patterns and distribution is unreliable. Once amyloid is histologically confirmed, further typing should be performed using mass spectrometry or IHC to guide clinical management.

Histologically, amyloid appears as pale or pink, homogeneous, and amorphous material on H&E stain. Congo red stain demonstrates the characteristic "congophilia," a red-orange appearance under light microscopy (Fig. 7C), with apple-green birefringence under polarized light. It shows a distinctive green color with sulfated Alcian blue stain, which does not require polarized light to visualize (Fig. 7E).

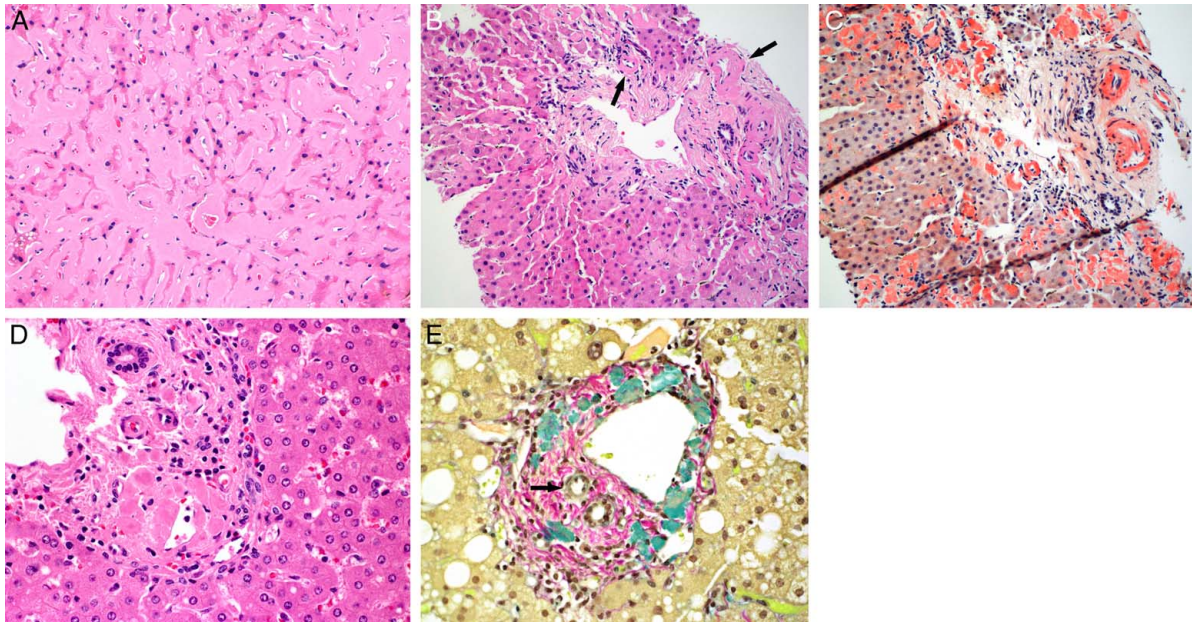

FIGURE 7. Hepatic amyloidosis. A, Sinusoidal linear pattern showing diffuse sinusoidal obliteration and marked hepatocyte atrophy (original magnification ×200). B, Vascular linear pattern showing involvement of hepatic artery branches in a portal tract (original magnification ×200). C, Congo red stain highlights amyloid deposits in hepatic artery branches, portal stroma, and sinusoids (original magnification ×200). D, Globular pattern showing globular amyloid deposits in a portal tract (original magnification ×400). E, Sulfated Alcian blue stain highlights globular amyloid deposits in a portal tract (original magnification ×400). Note that the hepatic artery (arrow) and portal vein are spared. Please see this image in color online.

Extracellular amyloid-like deposits, such as light chain deposition disease, Waldenstrom macroglobulinemia, and fibronectin are Congo red negative.[73,74] Clinical correlation and mass spectrometric analysis can further help the distinction. While both light chain deposition disease and AL amyloid involve abnormal light chains, the deposited light chains in the former do not aggregate to form amyloid fibrils.[75]

GAUCHER DISEASE

Gaucher disease is an autosomal recessive lysosomal storage disorder that affects multiple organs, including the liver, spleen, bone marrow, and central nervous system. Clinical manifestations include hepatosplenomegaly, bone marrow infiltration, coagulopathy, bone disease, skeletal deformities, and, in rare cases, neurological involvement.[76] The disease is caused by deficient lysosomal glucocerebrosidase (GBA) enzyme activity due to mutations in the *GBA* gene, leading to glycosphingolipid storage in cells of the mononuclear phagocyte system.[77]

Hepatic involvement ranges from subtle structural abnormalities, scattered foci of affected cells, to extensive replacement of liver parenchyma, advanced fibrosis, and cirrhosis.[78,79] The histologic hallmark is the presence of Gaucher cells, which are enlarged macrophages with eccentrically or centrally placed nuclei and abundant cytoplasm containing striated glucocerebroside deposits, resembling wrinkled tissue paper (Fig. 8A). This finding can be subtle as Gaucher cells can be sparse. In general, they are more abundant in zone 3, and less prominent in portal and periportal areas. Trichrome and PAS stains can help highlight the characteristic striations in the cytoplasm of Gaucher cells, which may also contain small amounts of iron deposits. Hepatocytes may exhibit atrophy or degenerative changes due to compression from enlarged aggregates of Gaucher cells. Perisinusoidal fibrosis is a common finding.[78] Cirrhosis or extensive replacement of liver parenchyma by Gaucher cells typically occurs in severe cases.

NIEMANN-PICK DISEASE

Niemann-Pick disease is a group of inherited lysosomal storage disorders classified into types A, B, and C based on genetic mutations and clinical presentation.[80] Types A and B are caused by mutations in the *SMPD1* gene, which encodes acid sphingomyelinase.[81] This enzyme hydrolyzes sphingomyelin and its deficiency leads to accumulation of sphingomyelin in lysosomes. Types A and B are distinguished by age onset and disease presentations. The former occurs in infancy with rapidly progressive neurodegenerative disorder. The latter is a chronic and progressive visceral disease with hepatosplenomegaly, progression to cirrhosis, and lung disease. Type B disease may also manifest as acute liver failure. Type C results from mutations in the *NPC1*, or less frequently, *NPC2* gene, leading to impaired intracellular cholesterol and lipid trafficking.[82] Mutations in these transporters lead to accumulation of cholesterol and lipids in endosomes and lysosomes.

The histologic hallmark of hepatic involvement is the presence of foamy cells, which are primarily enlarged, lipid-laden macrophages. These cells have abundant microvesicular cytoplasm with eccentrically or centrally located nuclei and are prominently distributed within portal tracts and sinusoids. Hepatocytes and bile duct epithelium also progressively accumulate lipid, leading to a foamy appearance indistinguishable from foamy macrophages.

Figure 8B illustrates a 5-year-old girl with obesity who presented with several days of fever and cough. Clinical workup revealed hepatosplenomegaly and mildly elevated liver enzymes. Imaging studies demonstrated pneumonia in the bilateral lower lobes. A liver biopsy was performed to evaluate for fatty liver disease, storage disease, and infections. Histologic examination of the biopsy revealed enlarged hepatocytes and scattered enlarged macrophages with abundant foamy cytoplasm. The macrophages were distinguished by their more swollen and pale appearance and can be easily recognized on PAS stain (Fig. 8C). There was no steatosis. Electron microscopy demonstrated cytoplasmic lysosomal figures, some with a lamellar internal configuration, as well as membrane-bound degenerative lipid particles of varying electron density. These findings were consistent with a lipid or lysosomal storage disorder. Subsequent lysosomal enzyme screening revealed low sphingomyelinase activity. Genetic testing identified two pathogenic variants in the *SMPD1* gene, confirming the diagnosis of Niemann-Pick disease, type B.

DUBIN-JOHNSON SYNDROME

Dubin-Johnson syndrome is an autosomal recessive disorder characterized by asymptomatic conjugated hyperbilirubinemia, typically presenting with normal liver enzyme levels and absence of other hepatobiliary disease

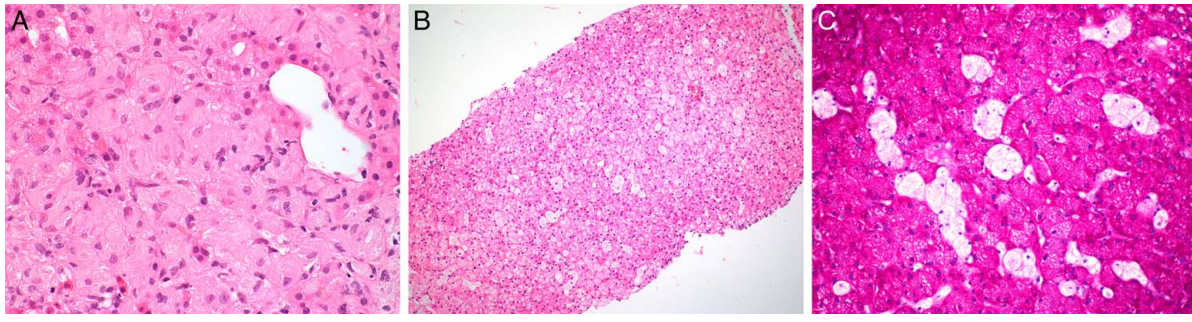

FIGURE 8. A, Gaucher disease showing Gaucher cells with a wrinkled tissue paper appearance (original magnification ×400). B, Niemann-Pick disease showing enlarged hepatocytes and scattered macrophages with abundant foamy cytoplasm (original magnification ×100). C, The macrophages are distinguished by their more swollen and paler appearance and can be easily recognized on PAS stain (original magnification ×200). Please see this image in color online.

features.[83] It is caused by mutations in the *ABCC2* gene, resulting in the absence of functional multidrug resistance protein 2 (MRP2) at the hepatocyte canalicular membrane. This defect impairs the excretion of conjugated bilirubin from hepatocytes, leading to its accumulation and subsequent conjugated hyperbilirubinemia.[84,85] The liver is distinctively pigmented and appears dark brown to black grossly. Histologic examination reveals coarse, dark brown granular pigment predominantly in centrilobular hepatocytes (Figs. 9A, B), though a diffuse lobular distribution can also be observed. The pigmented granules are accentuated by the PASD stain (Fig. 9C), and stain black with Fontana-Masson stain. They were initially thought to contain melanin or lipofuscin, but are currently believed to represent polymers of epinephrine metabolites.[86]

The differential diagnosis may include Gilbert syndrome, age-related, or drug-related lipofuscin deposition in hepatocytes. Gilbert syndrome, an autosomal recessive disorder caused by mutations in the *UGT1A1* gene, is characterized by intermittent unconjugated hyperbilirubinemia, often triggered by starvation or stress.[87] Lipofuscin deposition in these conditions also exhibits a centrilobular distribution, but the pigment is considerably less coarse.

HYPERVITAMINOSIS A (STELLATE CELL HYPERPLASIA)

Vitamin A is primarily stored in hepatic stellate cells (HSC; also known as Ito cells or perisinusoidal fat-storing cells) as retinyl esters. Excessive intake of vitamin A, whether through medications, supplements, or dietary sources such as fish oil or fish liver, can result in vitamin A overload. This leads to HSC hyperplasia and hypertrophy.[88,89] Activated HSCs may acquire a myofibroblast-like phenotype, characterized by the production of smooth muscle actin and extracellular matrix components, initiating the process of hepatic fibrosis.[90] Recruitment of inflammatory cells causing hepatocyte injury has also been reported in cases of hypervitaminosis A.[91] Liver injury due to vitamin A toxicity is well recognized as dose dependent and duration dependent. Clinical presentations range from

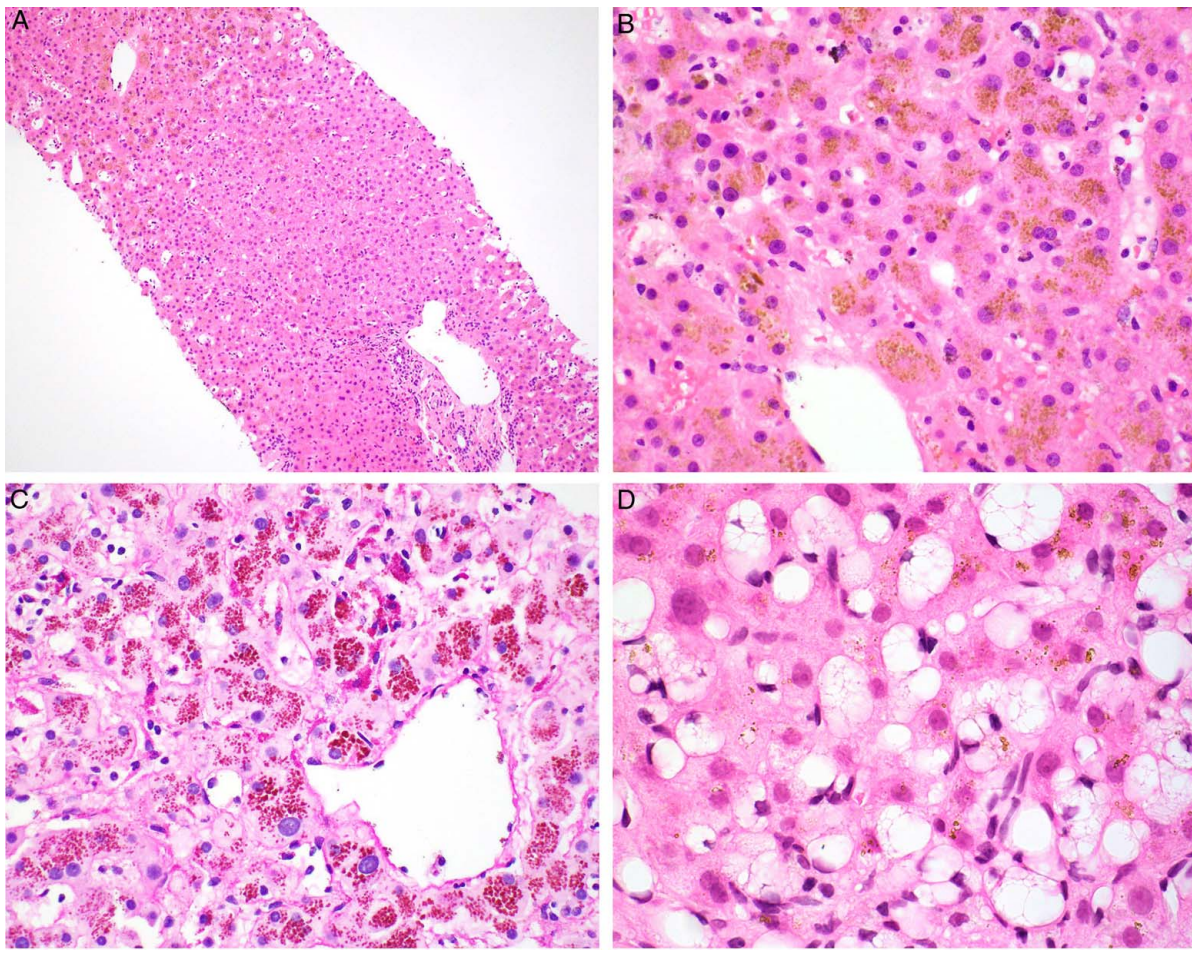

FIGURE 9. A, A liver biopsy from a patient with Dubin-Johnson syndrome showing near-normal histology (original magnification ×100). B, High-power view showing dark brown coarse granules in hepatocytes, mainly seen at centrilobular regions (original magnification ×400). C, The granules are more prominent on PASD stain (original magnification ×400). D, A liver biopsy from a patient who is an avid consumer of vitamins and herbal supplements. It shows cytoplasmic lipid vacuoles in stellate cells (original magnification ×600), supporting a diagnosis of hypervitaminosis A (courtesy of Dr. Kay Washington of Vanderbilt University). The biopsy also shows mild iron deposition. Please see this image in color online.

TABLE 1. Key histologic features of rare liver diseases with near-normal liver biopsy findings

Disease	Key Histologic Features
Wilson disease	No characteristic features
Hemochromatosis/hemosiderosis	Iron deposition in hepatocytes and/or Kupffer cells
α1-Antitrypsin deficiency	Cytoplasmic eosinophilic globules in periportal hepatocytes
Fibrinogen storage disease	Vague cytoplasmic eosinophilic globular inclusions in hepatocytes; fingerprint-like structures on electron microscopy
Glycogenic hepatopathy	Diffuse swollen and pale hepatocytes
Glycogen storage disease	Diffuse swollen and pale hepatocytes; Cytoplasmic glycogen inclusions (type IV)
Glycogen pseudo-ground glass change	Large, distinctive cytoplasmic eosinophilic/amphophilic inclusions in hepatocytes
Amyloidosis	Sinusoidal linear, vascular linear, and globular deposits; Positive Congo red staining
Light chain deposition disease	Sinusoidal linear deposits; Negative Congo red staining
Gaucher disease	Gaucher cells (macrophages) with wrinkled tissue paper appearance in cytoplasm
Niemann-Pick disease	Enlarged macrophages, hepatocytes, and bile duct epithelial cells with abundant foamy cytoplasm
Dubin-Johnson syndrome	Dark brown coarse granules in centrilobular hepatocytes
Gilbert disease	Increased lipofuscin in centrilobular hepatocytes
Hypervitaminosis A	Hyperplastic and hypertrophic hepatic stellate cells with lipid vacuoles
Hemophagocytic syndrome	Kupffer cell hyperplasia and hypertrophy with cytoplasmic engulfment of erythrocytes, leukocytes, platelets, and cell fragments
Nodular regenerative hyperplasia	Diffuse 1-3 mm regenerative nodules with compressed and atrophic hepatocytes in between
Obliterative portal venopathy	Narrowing or obliteration of portal veins
Vanishing bile duct syndrome	Bile duct loss
Alagille syndrome	Absence of bile duct in $>50\%$ of portal tracts
Cystic fibrosis	Inspissated secretion in bile ducts
Porphyrin metabolism disorders	Dark-brown protoporphyrin deposits in canaliculi with Maltese cross-like configuration under polarized light
Bland (pure) cholestasis	Zone 3 canalicular cholestasis
Resolving liver injury	Ceroid-laden macrophages in portal tracts and lobules

asymptomatic cases with persistently elevated liver enzymes to noncirrhotic portal hypertension and frank cirrhosis. Cases of liver cirrhosis caused by chronic hypervitaminosis A requiring liver transplantation have been documented.[90]

The diagnosis of hypervitaminosis A-related liver injury can be challenging, particularly in patients with limited clinical information regarding excessive vitamin A ingestion. The characteristic histologic feature is HSC hyperplasia and hypertrophy in the space of Disse. The affected HSCs become unusually enlarged with abundant cytoplasmic lipid vacuoles and compressed, peripherally located nuclei, resembling adipocytes (Fig. 9D). They may be focally or diffusely distributed within the biopsy. There may be minimal to mild portal and lobular inflammation, sparse apoptotic bodies, sinusoidal dilatation, varying degrees of fibrosis, and nodular regenerative hyperplasia.[92]

CONCLUSION

In summary, interpretation of liver biopsies with normal, nearly normal, or subtle histologic changes can be very challenging. This review focuses on a selected group of rare metabolic, storage, and inclusion liver disorders and highlights key clinical and pathologic features for their diagnosis (Table 1). Integrating biopsy findings with clinical history, laboratory data, and results of other relevant ancillary tests is crucial to the establishment of a specific diagnosis.

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