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Review

Diagnostic approach to patients with cholestatic jaundice

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Conjugated hyperbilirubinemia due to any form of hepatobiliary disease is essentially the result of impairment in bile formation and/or bile flow, a condi tion known as cholestasis[1,2]. Cholestatic jaundice is often accompanied by a broad spectrum of laboratory, clinical, and histological abnormalities. Laboratory abnormalities include increased serum levels of alkaline phosphatase and gamma-glutamyltransferase (GGT), and variable elevation of bilirubin, serum copper, ceruloplasmin, cholesterol, lipoprotein X, and serum bile acids, as well as of prothrombin time, which is corrected by vitamin K supplementation. There is minimal or no elevation of aminotransferases. Clinically, pruritus, fatigue, xanthomas, back pain from osteoporosis, pale stools, or even steatorrhea may be present, with evidence of fat-soluble vitamin deficiency. Histologically, conjugated hyperbilirubinemia is characterized by bile plugs (bilirubinostasis), feathery degeneration of hepatocytes (cholate stasis), small-bile-duct destruction, perich olangitis, portal edema, bile lakes and infarcts (typically with extrahepatic obstruction), and finally, biliary cirrhosis[1-3].

MECHANISM OF CHOLESTASIS

Bile formation originates in hepatocytes with the uptake and production of organic anions, bilirubin, and bile salts through diverse cellular transporters that may be either sodium-dependent or independent[4]. Bile salts taken up at the sinusoidal surface of the hepatocytes are generally conjugated to increase their water solubility and subsequently are excreted into the biliary tree at the apical (canalicular) surface. Secretion is achieved via the combined process of Na^+ coupled, carrier-mediated, or vesicular-transport systems[4]. Multiple factors contribute to the impairment of bile flow: Endotoxins are potent stimuli for activating cytokine production from macrophages [5,6] and have acute cholestatic effects on hepatic bile production[7]. Endotoxins and several proinflammatory cytokines [tumor necrosis factor (TNF)alpha, interle ukin (IL)-1, and IL-6 down-regulate hepatic transport mechanisms that determine bile acid-dependent bile flow, affecting both bile acid uptake and canalicular secretion[8, 9]. These proinflammatory cytokines also promote the expression of MHC class II molecules on target cells, thereby enhancing target antigen presentation[10]. Proinflammatory cytokines activate neutrophils and T and B cells, increase the expression of intercellular adhesion molecules (ICAMs), and may promote tissue damage by direct action. It is proposed that these portal tract inflammatory events can contribute to the down-regulation of hepatocel lular bile salt transport, and hence aggravate cholestasis. Unfortunately, there are few cases of cholestatic jaundice in which the specific cellular defect has been identified. For most cholestatic process, multiple defects may act in concert to produce disease.

EVALUATION OF THE PATIENT WITH CHOLESTATIC IAUNDICE

The first question to be resolved is whether the cholestasis results from intrahepatic or extrahepatic disease process, bearing in mind that several intrahepatic causes of cholestatic jaundice can mimic extrahepatic obstruction to varying degree[2,11]. Comprehensive clinical evaluation comprising the history, physical examination, and basic laboratory tests and the additional information provided by ultrasonography (US) or computed tomography (CT) are highly successful in making this important distinction (Figure 1). Clinically important clues to extrahepatic obstructions include abdominal pain, a palpable gallbladder or upper abdominal mass, evidence of cholangitis, and a history of previous biliary surgery. Clinical clues to intrahepatic

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cholestasis include pruritus, as in primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) patients[12]. Pruritus may be prominent in alcoholic hepatitis and has been reported in about 10% of patients with acute viral hepatitis[13].

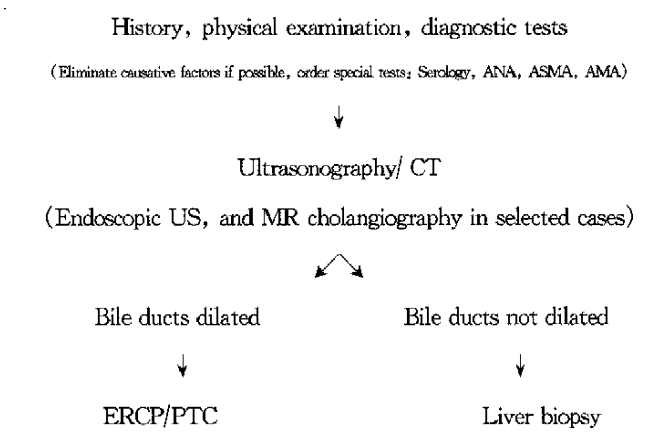

Figure 1 Schematic of work-up of cholestatic jaundice. AFP, alpha-fetoprotein; AMA, antimitochondrial antibodies; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; CT, computed tomography; ERCP, endoscopic retrograde cholangiography; MR, magnetic resonance; PTC, percutaneous transhepatic cholangiography; US, ultrasonography.

The patient should be asked about risk factors, including alcohol intake, medications, sexual contact, drug abuse, needle punctures, and travel history. The family history is of value in benign recurrent intrahepatic cholestasis (BRIC). Details regarding the onset of jaundice and its duration, whether intermittent or progressive, as well as its associated symptoms like darkening of the urine, acholic stools, arthralgia, rash, weight loss, fever, chills, and pain in the right upper quadrant should be obtained[3]. Physical examination should involve careful observation of stigmata of chronic liver disease, xanthelasma, clubbing, and lymphadenopathy. Hepatomegaly is usual in alcoholic liver disease, primary or secondary hepatic neoplasm, infiltrative disease, and primary biliary cirrhosis (PBC)[14,15]. Marked splenomegaly suggests cirrhosis with portal hypertension or lymphoproliferative disease[16,17].

Laboratory work-up for cholestatic jaundice should include complete blood count with differential, urea, creatinine, electrolytes, and a liver panel including alkaline phosphatase, GGT, aminotransferases, albumin, bilirubin, and prothrombin time. Immunological markers such as AMA, ANA, ASMA, ANCA, and immunoglobulins and serological markers for viral hepatitis are helpful. Serum alpha-fetoprotein, carcinoembryonic antigen, and CA19.9 may be increased in patients with malignancies[18].

Clinical evaluation is quite sensitive, but has a positive predictive value of only about 75%; that is, about 25% of patients with suspected obstruction actually have hepatocellular disease[2]. The rare case of obstruction that is missed in the initial clinical evaluation will probably become apparent on follow-up evaluation, and the delay in establishing the correct diagnosis is unlikely to harm the patient. If, on the other hand, obstruction is suspected, then a more aggressive work-up is appropriate.

US and CT have comparable sensitivity (85%-96%) in detecting dilatation of the intrahepatic and extrahepatic biliary tree in patients with proven obstruction[3]. US is widely recommended as the first-line imaging procedure in the evaluation of cholestatic jaundice. Although gallbladder stones are readily detected by US, common bile duct stones may be missed in 60% of patients because of the interference caused by intestinal gas. Obesity may also lead to an unsatisfactory study. Moreover, with the exception of mass lesion in the head of the pancreas, US usually does not identify the type of obstruction.

CT is more likely to yield information regarding the level of the obstruction, localizing this in 90% of patients[3,19]. CT is also a reasonable first choice in patients with lymphoma, in whom it may provide information regarding retroperitoneal lymph node involvement[20]. Although a negative US or CT may represent a logical stopping point in the diagnostic work-up of a patient in whom obstruction is not strongly suspected on clinical grounds, a negative study should not dissuade the clinician from further evaluation of a patient in whom obstruction is considered highly likely. In patients in whom the clinical suspicion of biliary obstruction is supported by CT or US, direct visualization of the biliary tree with percutaneous transhepatic cholangiography (PTC) orendoscopic retrograde cholangiography (ERCP) is appropriate and necessary. PTC and ERCP have in common 99% sensitivity and specificity for the diagnosis of biliary obstruction, and both are capable of demonstrating the site and the nature of the obstruction in more than 90% of patients[21]. Both also provide therapeutic interventions including removal of stones, dilatation of strictures, and the pl acement of stents across obstructing lesions, as well as the placement of biliary drainage catheters[22].

ERCP is the procedure of choice in suspected ampullary or duodenal lesions in pancreatic

carcinoma and when gallstone obstruction is suspected, in which case sphincterectomy and stone extraction can be implemented. Palliative stenting of neoplastic obstruction and temporary stenting of certain types of traumatic lesions of the common bile duct are frequently accomplished with ERCP [22]. ERCP is also a logical first procedure in patients with suspected PSC and in patients who have undergone cholecystectomy in whom jaundice is suspected on the basis of choledocholithiasis, since US is often unhelpful in this setting, as the stone is likely to be missed and ductal dilatation may be absent[23].

PTC is often preferred when an obstructing lesion high in the biliary tree is anticipated, as it will permit visualization of the proximal extent of the lesion and enable immediate biliary drainage of obstructed intrahepatic ducts. PTC is also preferred in patients with previous gastrointestinal surgery like Billroth II gastrectomy[24]. PTC is usually contraindicated in patients with mark ed ascites and coagulopathy. In some instances, both PTC and ERCP may be used to gether in a combined therapeutic approach from above and below to maneuver guidewires and stents across a difficult obstruction. Sometimes hepatobiliary scintigraphy, which is of established value in the diagnosis of acute cholecystitis, may help in evaluating biliary leaks and congenital malformations[25].

Recently, endoscopic CT and magnetic resonance cholangiography have been found to be very helpful in the diagnosis of biliary obstruction, especially in the setting of liver transplantation[26,27]. A negative study obtained by ERCP or PTC represents a reasonable endpoint to the work-up of obstruction in the jaundiced patient. Liver biopsy may be appropriate at this time point. Minor complications of a cutting needle biopsy, such as prolonged right upper quadrant pain, occur in up to 6% of cases[28]. Major complications such as clinically significant intra-abdominal bleeding are uncommon, and mortality (almost always from hemorrhage) is approximately 0.01%[29,30]. Cholestasis per se does not appear to increase the risk of a major complication. Percutaneous liver biopsy is contraindicated in patients with a significant coagulopathy or substantial ascites; in these instances, performance of a transjugular liver biopsy [31] or not performing a biopsy at all are alternatives. Weighing against these negative considerations are the potential benefits of obtaining histological information.

Liver biopsy may be of great value in differentiating hepatocellular cholestasis from obstructive cholestasis[32].Unfortunately, differentiating drug-induced cholestatic hepatitis from other causes cannot be performed histologically. A chief question in a patient with cholestatic jaundice is whether there is significant underlying chronic liver disease[33] or an infiltrative process, particularly granulomatous disease, lymphoma, or metastatic carcinoma[34]. Portal tract neutrophilic infiltrates seen in liver biopsy are a common accompaniment of biliary obstruction, ascending cholangitis, outright sepsis, cholangiolytic drug reactions, and hyperalimentation[35]. Finally, biopsy of the liver is particularly helpful in differentiating the cholestatic picture of alcoholic hepatitis from that of cholangitis[36].

DIFFERENTIAL DIAGNOSIS

Cholestatic liver disease can be broadly categorized as extra-or intrahepatic. The extrahepatic component is best approached anatomically. The intrahepatic component comprises intrinsic disease, infiltrative disease, systemic disease, and space-occupying lesions. Prevalent clinical abnormalities (Tables 1, 2) will be detailed in subsequent sections.

EXTRAHEPATIC CAUSES OF CHOLESTATIC JAUNDICE

Among the extrahepatic causes of chronic cholestasis, secondary sclerosing cholangitis due to choledocholithiasis or biliary surgery is probably the most common. This is usually related to a single stricture of the common hepatic duct or common bile duct. Other causes of extrahepatic cholestasis are listed in Table 1.

Table 1 Differential diagnosis of cholestasis and hyperbilirubinemia (cholestatic jaundice)

CBD dilated: Best approach is anatomically
Ampulla of Vater
Stones, carcinoma of pancreas, chronic pancreatitis, ampullary neoplasm, diverticulum, pancreatic cyst, abscess of pancreas, sphincter of Oddi dysfunction
Common bile duct
Benign traumatic stricture, stones, choledochal cyst, cholangiocarcinoma, parasites, hemobilia, extrahepatic atresia
Gallbladder
Carcinoma of gallbladder
Portal nodes
Cholangicarcinoma, lymphoma, metastatic carcinoma, cavernous portal vein

CHOLEDOCHOLITHIASIS

Although gallstones produce jaundice by impaction in the common bile duct, acute cholecystitis is associated with mild jaundice in up to 20% of

patients. This is attributed to edema of the common duct (Mirizzi syndrome) or to direct involvement of the porta hepatis by inflammation[37]. Common duct stones retained after cholecystectomy may produce jaundice in the immediate postoperative period or even several years after cholecystectomy. Acute gallstone obstruction is often associated with pain from biliary colic or from acute pancreatitis resulting from ampullary obstruction. Sudden impaction of a stone in the common duct may be associated with a rapid rise in aminotransferases 20-50 above normal, followed by an equally rapid decline within 72 hours [38]. Cholangitis is rel atively common in patients with choledocholithiasis and manifests as fever with chills, abdominal pain, and jaundice, a syndrome known as Charcot's triad, although jaundice may be absent in one third of patients with cholangitis[39].

BENIGN STRICTURES OF THE BILE DUCTS

Benign biliary stricture in adults following previous surgery and biliary atresia in the pediatric population are the two most common type of strictures[18]. PSC may produce multiple or diffuse strictures that are not associated with proximal ductal dilatation[40]. In patients with chronic alcoholic pancreatitis, a long stricture may develop in the intrapancreatic portion of the common duct, leading initially to cholestasis and eventually to secondary biliarycirrhosis[41]. Ampullary stenosis may result in patients with acquired immunodeficiency syndrome (AIDS)[42] or from the trauma of passing a stone. Cholangitis is frequent in patients with benign biliary obstruction, in contrast to its relative infrequency in the framework of malignant obstruction[18].

NEOPLASTIC OBSTRUCTION

Pancreatic carcinoma is the commonest neoplasm producing obstructive jaundice. Other tumors include cholangiocarcinoma, ampullary tumors, and carcinoma of the gallbladder[18,43]. Abdominal pain radiating into the back, along with loss of appetite and weight loss, may be present, but jaundice may also develop without pain (usually progressive and deep jaundice). Cholangiocarcinoma may obstruct the biliary system at any level, and the clinical presentation is similar to pancreatic cancer[44]. Cholangiocarcinoma of the extrahepatic bile ducts may be growing into the lumen. The sclerosing variant of cholangiocarcinoma, which frequently arises at the confluence of the right and left hepatic ducts (Klatskin's tumor), may be difficult to distinguish from PSC both radiologically and on biopsy. This tumor infiltrates early into the wall of the bile duct, where it elicits a markedly sclerotic response[45].

Tumors producing complete obstruction of the common bile duct may be accompanied by marked, palpable dilatation of the gallbladder (Courvoisier's law). Ampullary tumors may produce intermittent jaundice because of sloughing of the tumor and partial relief of the block. Metastatic cancer may obstruct the bile duct, as may lymphoma[46]. Hepatocellular carcinoma may uncommonly rupture into the biliary system and give rise to tumor emboli that lodge in and obstruct the common duct[47]. The extrahepatic ducts may be compressed by adjacent tumor, by peribiliary lymph node infiltrated by lymphoma, or by metastatic carcinoma of breast[46]. Direct infiltration of the ducts by lymphoma may also lead to obstruction[48].

UNCOMMON CAUSES OF OBSTRUCTIVE JAUNDICE

Choledochal cyst may first manifest as obstructive jaundice after 17 years of age[49]. A duodenal diverticulum is a rare cause of biliary obstruction. Hemobilia, mostly a result of hepatic trauma, including invasive procedures or neoplasm, presents with the triad of biliary colic, jaundice and gastrointestinal bleeding[50]. Invasion of the common bile duct with Ascaris or with liver flukes of the Fasciola, Clonorchis, or Opisthorchis genera may produce cholangitis[51]. Secondary sclerosing cholangitis due to opportunistic infection of immunodeficient patients has become increasingly common since the advent of AIDS. Cryptosporidium parvum, cytomegalovirus (CMV), and Microsporidia- are the organisms most frequently found[52].

INTRAHEPATIC CAUSES OF CHOLESTATIC JAUNDICE

Intrahepatic cholestasis may arise from many sources and presents, therefore, a particular challenge when it develops in the seriously ill patient (Table 2). Many insults may cause local and systemic activation of the inflammatory cytokine system, and thus these proinflammatory events are potent inducers of intrahepatic cholestasis.

INTRINSIC DISEASES

Drug-induced cholestasis. Drugs may be responsible for 2%-5% of cases of jaundice in in-patients, and this percentage is probably substantially higher in the elderly[53]. The clinical presentation may mimic viral hepatitis or biliary tract disease. Serum sickness like features, including rash, arthralgia, and eosinophilia, are clues to a drug-induced etiology[53]. Chronic cholestasis tends to occur as a rare idiosyncratic reaction to certain commonly used drugs, including ampicillin-clavulanic acid,

chlorpromazine, cotrimoxazole, erythromycin, flucloxacillin, phenytoin, and tetracycline (Table 3)[54]. The histological features vary from case to case and over time. Generally, in the acute phase there is parenchymal bilirubinostasis, in the chronic phase bilirubinostasis commonly resolves, and features of cholate stasis persist and ductopenia develops[55].A different pattern of drug-induced liver injury leading to chronic cholestasis is drug-induced sclerosing cholangitis, as seen following floxuridine treatment[56]. Scolicidal agents, injected into intrahepatic hydatid cysts, may escape into the biliary system and cause stricture formation that may ultimately lead to biliary cirrhosis[57]. In patients taking numerous medicines, the only practical approach is to eliminate the drug with the highest likelihood of cholestatic injury and monitor for improvement.

Table 2 (continued): Differential diagnosis of cholestatic jaundice

Normal CBD	
Extrahepatic	
	Stone too early, stone too late, cholangiocarcinoma, and primary sclerosing cholangitis
Intrahepatic	
	Intrinsic diseases
	Drugs, alcoholic hepatitis, viral hepatitis, AIDS, primary biliary cirrhosis, autoimmune cholangitis, primary sclerosing cholangitis, idiopathic adulthood ductopenia, Autoimmune hepatitis, decompensated liver cirrhosis
Infiltrative diseases	
	Granulomatous hepatitis (Tuberculosis, amyloidosis), sarcoidosis, Lymphoma, leukemia, fatty liver
Systemic diseases	
	Sepsis, total parenteral nutrition (TPN), benign recurrent intrahepatic cholestasis (BRIC), cholestasis of pregnancy, cystic fibrosis, disappearing intrahepatic ducts syndrome, allograft rejection, graft versus host disease (GVHD), sickle cell syndrome, mastocytosis, hypereosinophilic syndrome, Hyperthyroidism
Space occupying lesions	
	Blood-hematoma, peliosis; pus-bacterial, amebic; cyst-hydatid, polycystic Cancer-primary, secondary

Table 3 Common drugs known to cause cholestatic jaundice

Antimicrobial agents	
	Augmentin (amoxicillin-clavulanic acid), cloxacillin, erythromycin, ethambutol, dapsone, fluconazole, nitrofurantoin, griseofulvin, ketoconazole, terbinafine
Cardiovascular agents	
	Disopyramide beta-blockers, ACE inhibitors, propafenone, ticlopidine, warfarin, methyldopa
Endocrine agents	
	Sulfonylureas, clofibrate, estrogens, tamoxifen, androgens, niacin, oral contraceptives
Gastrointestinal agents	
	H2 blockers (e.g., ranitidine), penicillamine
Immunosuppressive agents	
	Azathioprine, cyclosporine, gold salts, NSAIDs (e.g. diclofenac, nimesulide, piroxicam)
Psychopharmacologic agents	
	Tricyclic antidepressants, benzodiazepines, phenothiazines, phenytoin, halothane

ACE: angiotensin-converting enzyme; NSAIDs: non-steroidal anti-inflammatory drugs.

Alcoholic hepatitis. Alcoholic hepatitis with severe cholestasis m ust always be considered. Marked hepatomegaly with hepatic tenderness and evidence of hepatocellular failure (aminotransferases <500U/L), along with a compatible history of alcohol intake and fever, suggests the diagnosis. Alkaline phosphatase can vary from normal to values in the thousands U/L. Bilirubin levels range from normal to 340 μmol/L • 510 μmol/L[58].

Viral hepatitis. Infrequently, a severe cholestatic syndrome may follow the acute phase of viral hepatitis; this is most commonly seen with hepatitis A[59], Hepatitis C[60], and hepatitis E[61]. Despite the fact that jaundice may be profound for up to 6 months, complete recovery is the rule. Recently, we described a case of severe cholestatic jaundice in the elderly due to Epstein-Barr virus infection, which led to a diagnostic delay since the clinical presentation mimicked biliary obstruction[62].

AIDS. In AIDS-related cholangiopathy, *Cryptosporidium* is the most frequent cause, but *Microsporidia*, CMV, *Mycobacterium avium*-complex, and Cyclospora have also been reported. Papillary stenosis may be present in patients with CD4 lymphocyte counts of <100/mm[3] and alkaline phosphatase >500IU/L.Jaundice is an unusual manifestation of AIDS-related cholangiopathy. If present, it suggests other disorders, including drug or alcohol abuse or neoplasm[63].

Primary biliary cirrhosis. PBC could account for cholestatic jaundice. Classic PBC is described as a chronic non-suppurative cholangitis associated with AMA positivity in 95% of cases (anti-M2). Thirty percent will have positive ANA[64]. Histolog ically, bile duct injury along with portal inflammation are the usual findings, which are most often associated with elevation in alkaline phosphatase, IgM, and cholesterol. A female predominance is characteristic. Patients may, most commonly, be asymptomatic at presentation or may describe fatigue, pruritus, or right upper quadrant pain. Less than 20% of patients will have jaundice at time of presentation, and less than 5% will exhibit complications of portal hypertension[64]. The majority of patients will have associated autoimmune disorders (Sjögren's syndrome, scleroderma, and arthritis). Ursodeoxycholic acid (UDCA) is the only drug shown to prolong survival and to improve biochemical abnormalities. However, there is no evidence that it improves liver histology[65]. Presentation of HLA-II antigens as well as the expression of ICAM-1 and LFA3 induced by proinflammatory cytokines like TNF-alpha and interferon-gamma appear to

contribute to the biliary cell lysis observed in PBC[66].

Autoimmune cholangitis. AIC is a recent entity inwhich liver biopsy findings are indistinguishable from classic PBC, but AMA positivity is lacking. Clinical and biochemical parameters are similar to PBC, except that in AIC other autoantibodies such as ANA and ASMA are often found in varying titers. The IgM titers are typically lower as well. These patients are treated as if they have PBC[67].

Primary sclerosing cholangitis. PSC patients are more likely to be young men. PSC is associated with inflammatory bowel disease in 40% of cases [68]. Current information suggests immune-mediated damage of the biliary epithelium, although a precise mechanism has not been defined. Patients typically present with cholestasis, although occasionally jaundice and less commonly portal hypertension are present. Serum ANCA is positive in up to 80% of patients[69]. Both intra and extrahepatic bile ducts are involved, although a small percentage of patients have their disease confined to the hilar extrahepatic duct. Liver histology is not particularly useful in making the diagnosis, but does aid in the diagnosis of small-duct PSC (pericholangitis). Recurrent bacterial cholangitis as well as the development of cholangiocarcinoma and (in 15%-30% of cases) carcinoma of the colon constitute the morbid complications[70]. UDCA has no benefit in these patients regarding survival and quality of life. Whether other therapies such as FK-506 and colchicine offer significant benefit has not been established[71].

Idiopathic adulthood ductopenia. This entity is rare and is defined by the presence of ductopenia (decrease of bile ducts in >50% of the portal triads) and cholestasis in the absence of known cholestatic liver disease. It is a diagnosis of exclusion[72]. In addition to ductopenia, the biopsy may show lymphocytic cholangitis and features of chronic cholestasis. In some patients the process progresses to biliary cirrhosis. A recent report suggests that UDCA may result in biochemical improvement[72].

Autoimmune hepatitis. AIH can present as a primary cholestatic disorder[73]. By the criteria proposed by the International Autoimmune Hepatitis Group, a score can be calculated that defines the probability of a diagnosis of AIH. Patients are usually females (70% of cases) ANA and ASMA are present in the serum of the majority of patients. Furthermore hypergammaglobulinemia is present in 80% of cases. Associated autoimmune disorders include arthritis, rash, thyroiditis, Sjögren's syndrome, and ulcerative colitis[74].

Decompensated chronic liver disease. Jaundice may occur during the course of chronic hepatitis or cirrhosis. In cirrhosis, jaundice often is accompanied by other evidence of severe hepatocellular dysfunciton and is a prognostically grave sign. Cirrhosis induced by extrahepatic obstruction is associated with increased levels of circulating endotoxins[75], and elevated levels of proinflammatory cytokines can be documented in patients with cirrhosis of biliary or viral origin[76].

INFILTRATIVE DISEASES

Granulomatous hepatitis. GH is a common cause of cholestatic liver disease. Most often the liver manifestations are secondary to a more disseminated process , but isolated GH has been described[77]. GH is a well-described entity associated with a long list of causes, including sarcoidosis, infection (tubercular and fungal, especially histoplasmosis), hypersensitivity reaction, foreign-body reaction, malignant conditions, inflammatory bowel disease, drug reaction, and as a manifestation of other chronic liver disease[77]. In one series, approximately 20% of cases of patients with granulomas were attributed to asso ciated liver conditions. On the other hand, idiopathic GH accounts for 5%-36% of cases in which hepatic granulomas are found [78]. Pathologically, hepatic granulomas are usually multiple nodular infiltrates consisting of aggregates of epithelioid cells or macrophages surrounded by a rim of mononuclear cells. Mult inucleated giant cells are sometimes present. The normal architecture of the liver is usually not disturbed. In some cases, granuloma may be confined to the liver with no evidence of extrahepatic granulomatosis. Clinically, patients are often asymptomatic, and granulomas are found as part of a work-up for abnormal liver function tests or in the evaluation of fever of unknown origin (FUO). In studies of FUO, GH accounts for up to 13% of cases[79]. In GH, non-specific s ymptoms are the rule, usually including malaise, anorexia, and fever. Manifestat ions of profound cholestasis or hepatic failure are rare [77]. In such ca ses, routine bacterial and fungal blood culture as well as special culture and s tains of involved tissue would be required. GH tends to follow a benign course,with spontaneous recovery in most cases.

Sarcoidosis. Sarcoidosis is a systemic disease characterized by non-caseati nggranuloma of multiple organs. Seventy percent of patients have hepatic granuloma. Localization of portal granuloma may result in cholestasis with destruction of interlobular bile ducts[80]. A non-caseating granuloma indicates a combined role of activated CD4 T cells and macrophages. Elevated alkaline

phosph atase is the most characteristic abnormality found on liver testing and may be reduced by treatment with corticosteroids used to treat other manifestations of the disease. Concomitant intrathoracic disease, pulmonary symptoms, and significant anemia/leukopenia make this diagnosis very likely[81].

Lymphoma. Between 3% and 10% of patients with lymphoma develop jaundice duri ng the course of their disease and its treatment[82]. The causes of jaun dice include hepatic infiltration, portal tract destruction, obstruction of the extrahepatic biliary tree, and jaundice associated with chemotherapy[82]. Histiocytic lymphoma may produce a rapidly progressive syndrome characterized by fever, hepatosplenomegaly, deep jaundice, lymphadenopathy, and pancytopenia. A rare syndrome of lymphoma[a2]associated idiopathic cholestasis has been reported most commonly with Hodgkin's disease, but may also occur with non-Hodgkin's lymphoma[84].

Fatty liver. Fatty liver, or non-alcoholic steatohepatitis, most commonly occurs in middle-aged women with obesity, diabetes, and hyperlipidemia and a variety of other medical problems. Cholestasis can be seen in about 5% of patients wi th fatty liver[85].

SYSTEMIC DISEASES

Bacterial infection (sepsis). Mild hyperbilirubinemia develops in 1%-6% of patients with bacterial infections. The bilirubin is usually <170 μmol/L. Serum a lkaline phosphatase levels range from 1.5 to 3-fold above normal, whereas serum aminotransferases usually show less than a 2-fold increase[86]. The or ganisms most commonly associated with infections producing cholestatic jaundice are the gram-negative bacteria. Gram-positive infection from Staphylococcus aureus,in particular toxic shock syndrome and streptococcal pneumonia, may also be associated with jaundice[86]. The pathogenesis of cholestasis in sep sis is unclear, but direct hepatotoxicity from gram-negative bacterial endotoxins,gram-positive bacterial lipoteichoic acid, hepatic hypoxia, destruction of tr ansfused red cells, and hematomas may all play arole. Endotoxins and inflammati on-induced cytokines such as TNF are potent cholestatic agents[87-90]. Bile may also precipitate within larger intrahepatic bile ducts in conditions in which sepsis is playing a role, producing massive ductular dilatation with retai ned bile at the interface of the hepatic parenchyma and portal tracts, so-called "cholangitis lenta"[91]. Other uncommon infections may produce cholestatic jaundice include leptospira, clostridium, and borrelia.

Total parental nutrition. TPN-associated cholestatic jaundice in adults usually follows infusions containing in excess of 60% of calories as lipids for a period longer than 3-4 weeks. Gallbladder stasis is almost universal in patients on TPN, with a marked increase in the incidence of gallstones[92]. If the TPN cannot be discontinued, it should be cycled around 10 hours per day. Excess caloric infusion can be avoided by keeping glucose <6 g/kg per day and lipid <2 g/kg per day. Recent reports have demonstrated improvement in cholestatic param eters by administration of UDCA[93]. Patients receiving hyperalimentatio n are susceptible to developing cholestasis because of the diminished stimulus to bile flow associated with the absence of oral feeding and release of hormones that stimulate bile flow[94], as well as the direct oxidant stress to th e liver. Whether there are toxic effects of the hyperalimentation solutions hasnever been clearly established[95]. However, hyperalimentation fluids are hypertonic and may aggravate a cholestatic state by further desiccating bile t hrough osmotic effects[95].

Benign recurrent intrahepatic cholestasis. BRIC is characterized by recurrent episodes of jaundice with pruritus, biochemical signs of cholestasis, and hist ological hepatocanalicular bilirubinostasis, with normal intra- and extrahepatic bile ducts and absence of inflammation and fibrosis, absence of factors known to produce intrahepatic cholestasis such as drugs or pregnancy, and symptom-free intervals[96]. Cholestatic episodes may last for many months. BRIC may occur in sporadic or familial form; the latter has recently been attributed to ge netic abnormalities on chromosome 18[97]. As in Byler disease, GGT is no rmal in the presence of high alkaline phosphatase. The episodes eventually resol ve without morphological sequelae.

Cholestasis of pregnancy. This entity occurs recurrently in the third trimester of pregnancy in susceptible individuals and resolves after parturition. It is characterized by biochemical cholestasis with pruritus, usually accompanied by jaundice. Contraceptive drugs are a risk factor. Histology of the liver is similar to BRIC. It is associated with increased risk of premature delivery or stillbo rn births[98]. UDCA has been used with success[99].

Cystic fibrosis. In the liver, mutation and deletion in cystic fibrosis tran smembrane conductance regulator impair biliary secretion and result in cholestas is in 15% of cystic fibrosis patients[100]. UDCA also may be useful in these cases[101]. Biliary cirrhosis occurs in approximately

5% of patients and affects more males than females[100].

Disappearing intrahepatic bile ducts. Disappearance of intrahepatic bile ducts occurs in a variety of congenital and disease conditions (Table 4). The pathogenic mechanism responsible for bile duct destruction remains poorly defined. M oreover, it is likely that multiple mechanisms are operative in individual diseases. The primary mechanism includes direct or indirect cytotoxicity of biliary epithelial cells, ischemic injury and necrosis, and progressive obliterative perib iliary fibrosis[102].

Table 4 Causes and syndromes of ductopenia in the adult patient

Syndromatic ductopenia (Alagille syndrome)
Non-syndromatic adult ductopenia
Ductal plate malformation (congenital hepatic fibrosis, biliary atresia
Primary biliary cirrhosis, autoimmune cholangitis
Primary sclerosing cholangitis
Chronic rejection
Graft-versus-host disease
Sarcoidosis
Cystic fibrosis
Byler disease (progressive familial intrahepatic cholestasis)
Histiocytosis X and
Different drugs (amoxicillin-clavulanic acid, carbamazepine)
Duct destruction after regional chemotherapy (e.g. floxuridine)
Idiopathic adulthood ductopenia

Allograft rejection. Causes of cholestasis after liver transplantation are multifactorial, including postoperative dysfunction of the biliary tree (ductularor vascular), infection, recurrence of the primary disease, drugs, and rejection . In both acute and chronic rejection, small bile ducts are destroyed, resulting in cholestatic changes. Alkaline phosphatase, bilirubin, and GGT, along with am inotransferases, are elevated. Because of their lack of specificity, histological evaluation is needed to make the diagnosis[103].

Graft-versus-host disease. GVHD is the major complication of allogeneic bone marrow transplantation. Donor T cells recognize foreign host antigens in an immunocompromised host, resulting in injury to skin, intestine, and liver. In liver,the small bile duct cells are the primary targets of injury. The diagnosis is based on the development of rash, diarrhea, and elevated alkaline phosphatase. Acute GVHD usually begins in the third week, whereas chronic GVHD develops at around the sixth month after transplant. The extreme hyperbilirubinemia seems out of proportion to the degree of bile duct or hepatocellular damage[104]. Although liver biopsy can be performed, skin or rectal biopsy is preferred.

Sickle cell anemia. In patients with sickle cell anemia, jaundice may occur from a variety of factors, including viral hepatitis, choledocholithiasis, hepat ic sickle cell crisis, and a syndrome of severe intrahepatic cholestasis. Hepati c sickle cell crisis is characterized by severe right upper quadrant pain, fever, leukocytosis, jaundice, tender hepatomegaly, and moderate elevation of alkaline phosphatase. Resolution of acute symptoms with hydration and analgesia may befollowed by persistent cholestatic jaundice for several weeks[105].

Postoperative jaundice. The prevalence of jaundice following major surgery has been estimated at 17% for bilirubin levels of 2 mg/dl-4 mg/dl, with 4% of patientsd eveloping more pronounced elevations. The etiology of cholestatic jaundice in th e postoperative period may be discrete or multifactorial. Responsible factors in clude sepsis, drug- oranesthetic-induced hepatitis, and obstruction of the biliarytree resulting from pancreatitis, choledocholithiasis, or direct injury to the biliary tree[106]. The entity termed "benign postoperative cholestatic jaundice" occurs between 1 and 10 days following major surgery. The jaundice may be profound, with a 2 to 4-fold elevation of alkaline phosphatase levels and only mild increases in serum aminotransferases. Liver biopsy reveals cholesta sis without inflammation. The condition is self-limited and requires differentiation from obstructive jaundice[106].

Sweet's syndrome. This is an idiopathic condition, but approximately 20% of patients have an associated malignancy[107]. The disease is thought to be a hypersensitivity reaction, either as a parainflammatory (e.g., infections, a utoimmune disorders, vaccination) or paraneoplastic event. The most frequently observed neoplasm is acute myelogenous leukemia; lymphomas, chronic leukemia, mye lomas, myelodysplastic syndromes, and a variety of solid tumors also are represe nted. The onset of Sweet's syndrome is widely distributed around the time of de velopment of malignancy, appearing most often within 2 months before or after the clinical diagnosis of overt malignancy. A definitive derangement in neutrophil function in Sweet's syndrome has not been identified. Rather, elevated levels of circulating granulocyte colony-stimulating factor and IL-6 or of local cytokine s have been implicated[108-110].

OTHER INTRAHEPATIC CAUSES OF CHRONIC CHOLESTASIS

Nodular regenerative hyperplasia (NRH), bone marrow transplant (BMT), connective tissue diseases (CTD), Felty's syndrome, mastocytosis,

hypereosinophilic s yndrome, hyperthyroidism, and space occupying lesions that can lead to chronic intrahe patic cholestasis are listed in Table 1. The pathology of these entities isnot discussed further here.

CONCLUSIONS

The causes of cholestatic jaundice can usually be identified if one keeps in mind the important steps of transport of bilirubin and secretion of bile flow through the intra and extrahepatic biliary tree.

Most causes of cholestatic jaundice are a result of diseases of the liver or bil iary tract, including intrahepatic forms caused by drugs, alcohol, infection, and destruction of the interlobular ducts. In postoperative jaundice, multiple mec hanisms, such as a combination of pigment load with hypoxic injury to the liver, can result in jaundice. It is easy to visualize how mechanical obstruction of t he biliary tree will give rise to jaundice, as in a patient with carcinoma of the bile duct or PSC. There is no substitute for a good history, physical examinat ion, and review of the standard chemistries. With the initial information, the correct diagnosis can be made 85% of the time. In the remaining cases, non-invasive scanning procedures will help in confirming suspicions, but the final diagnosis will usually be made only with direct forms of cholangiography and/or liver biopsy.Occasionally we encounter a case of cholestatic jaundice where we cannotreadily establish the diagnosis. Tincture of time generally will lead to the ap pearance of further signs and symptoms that eventually will clarify the disease.

In every case, the responsibility rests on the physician to adopt a thoughtful a pproach to minimize risk, expense, and time involved in obtaining sufficient inf ormation for a definitive diagnosis and treatment.

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