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Approach To A Patient With Elevated Serum Alkaline Phosphatase

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The term cholestasis is derived from the Greek word “chole” which means bile and “stasis” meaning standing still. Cholestasis develops either due to a defect in bile synthesis, impairment in bile secretion or obstruction to bile flow. Cholestasis may occur as a result of an acute or chronic process involving either the extrahepatic or intrahepatic biliary tree [(1)]. This syndrome is characterized by an elevated serum alkaline phosphatase (AP) and gamma-glutamyltransferase (GGT) out of proportion to elevation of aminotransferase enzymes [(1)]. Clinically, pruritus and fatigue are the most common presenting symptoms of chronic cholestatic disorders. Key elements to the diagnostic workup include visualization of the biliary tree by cholangiography and evaluation of liver histology. Recent advances in understanding the genetic factors and immune mechanisms involved in the pathogenesis of cholestasis will hopefully lead to newer therapeutic interventions in the treatment of these diseases.

Representative case

A 68 yr old man presented with history of right upper quadrant pain. He described the pain as a dull aching sensation present intermittently for the past two years. He also reported a 20 pound weight loss and intermittent episodes of dark colored urine and pale stools. He denied taking any medications or excessive alcohol consumption. He had no other significant past medical history. The physical examination revealed jaundice and mild tenderness in the right upper quadrant but was otherwise normal. Laboratory tests revealed an elevated serum total bilirubin of 2.7mg/dl, AP of 437 U/L, alanine aminotransferase (ALT) of 85 U/L, aspartate aminotransferase (AST) 54 U/L. Computed tomography (CT) of the abdomen revealed mild prominence of extrahepatic bile ducts in the porta hepatis and intrahepatic biliary ductal dilation in both lobes with a patchy distribution; Endoscopic retrograde cholangiopraphy (ERCP) confirmed multifocal intrahepatic biliary ductal strictures with beading and focal dilatation and was reported to be consistent with sclerosing cholangitis. Cytology from the brushings was negative for malignancy. A liver biopsy revealed hepatic parenchyma with moderate to marked mixed portal inflammation, consisting of lymphocytes and plasma cells. Immunostain for IgG4 revealed numerous scattered IgG4-positive plasma cells in portal

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tracts up to 20/hpf. The serum IgG4 level was 320mg/dl. A diagnosis of IgG4-related autoimmune cholangitis was established and patient was started on corticosteroid therapy.

Physiology of Bile Formation

Bile acids are the predominant organic solutes in the bile and the driving force for the generation of bile flow. Conjugated bile acids, which represent the major fraction of bile acids in the blood, are transported across the basolateral membrane of hepatocytes by two distinct basolateral transporters: Na+-dependent transport represented by NTCP (*SLC10A1,* Sodium Taurocholate Co-Transporting polypeptide) and Na+-independent transport mediated by OATPs (organic anion transporting proteins OATP2, *SLC21A6*) [(2)]. NTCP is exclusively expressed in hepatocytes and is involved in the transport of both conjugated and unconjugated bile acids [(3)]. OATP on the other hand facilitates uptake of both conjugated and uncongugated bile salts, and also other organic anions and xenobiotics [(4)]. Therefore these uptake and export transporters are essential not only for bile synthesis, but also hepatic elimination of various xenobiotics including bile salts, bilirubin, cholesterol and drugs. Bile acids are actively transported across the hepatocyte canalicular membrane into the bile by these transporters. Bile acid efflux is mediated by a superfamily of ATP- binding cassette (ABC) transporters. The predominant ABC transporter has been identified as BSEP (*ABCB 11,* bile salt export pump) which mediates export of bile acids [(5)]. Some of the other ABC transporters identified include multidrug resistance associated protein MRP2 (*ABCC2*, efflux of multiple organic anions including bilirubin); multidrug resistance protein MDR1 (*ABCB1*, exports organic cation); and MDR2 (*ABCB4*, phospholipid export pump) [(6)]. In addition MRP2 also plays an important role in detoxification via its role in transport of drugs including chemotherapeutic agents, antibiotics and toxins [(7)]. MDR3 (multidrug resistance P-glycoprotein 3, *ABCB4*) is a special ABC transporter which flips phosphatidylcholine, a major lipid constituent, from the inner to the outer leaflet of the canalicular membrane into bile [(8)]. The expression of these transporters is tightly controlled to prevent accumulation of toxic bile acids in hepatocytes. The primary hepatic bile excreted by the hepatocytes into the bile canaliculus undergoes modifications during its passage through the biliary tree. Cholangiocytes take up bile salts via ASBT (the apical sodium-dependent bile salt transporter ASBT (*SLC10A2*) allowing intrahepatic cycling of bile salts [(9)].

Furthermore, the cholangiocyte transporters, chloride-bicarbonate anion exchanger 2 (AE2, *SLC10A2*) and cystic fibrosis transmembrane conductance regulator (CFTR, *ABCC7*), add cholangiocellular bile to hepatocellular bile. However, the most critical step in bile acid homeostasis, and a major determinant of bile acid pool size, is the intestinal reabsorption of bile salts [(10)]. Bile acids are re-absorbed into ileal columnar epithelium (via ASBT) and effluxed into the portal circulation (via MRP3) from where the hepatocytes then extract the bile salts completing the enterohepatic circulation [(11)]. The bile acid transporters are subject to extensive regulation at both the transcriptional and posttranscriptional level [(12)]. Nuclear receptors (NR) play an important role in bile acid metabolism and are activated by different compounds to promote transcription. The known NR include: farnesoid X receptor(FXR), pregnane X receptor(PXR), vitamin D receptor(VDR) and constitutive androstane(CAR) receptor. During cholestasis both FXR and PXR are activated, resulting in down regulation of *CYP7A1* and thereby decreased conversion of cholesterol to bile acid and decreased bile acid synthesis [(13)]. FXR is involved in up regulation of BSEP and down regulation of hepatic transporters NTCP. PXR activates Oatp2 whereas CAR regulates MRP2 and MPR3 [(14)]. Taken together, activation of NR results in decreased bile acid synthesis and uptake and increased bile acid efflux, thereby preventing further accumulation of toxic bile salts in the hepatocytes.

Pattern of Liver Test Abnormalities in Cholestasis

Liver disease is often reflected by elevation in liver enzymes and/or liver function. The term "Liver function test (LFT)" is a misnomer as these tests do not reflect liver function and may be abnormal in conditions unrelated to liver diseases. "LFT's" are often used to describe both serum liver enzymes (aminotransferases, AP) and true function tests such as prothrombin time, bilirubin and albumin. The pattern of liver enzyme abnormalities may help in characterizing the disease as hepatocellular, cholestatic, mixed or infiltrative (Table 1).

Persistent elevation of serum AP is frequently encountered and can pose a diagnostic dilemma. The highest concentration of AP is present in liver and bone; an elevated AP concentration is therefore generally attributed to either liver or bone disease. However, AP is also present in other organs including intestine, kidney, placenta and leucocytes. Serum AP levels vary with age, gender and blood type [(15)]. Mild elevation of AP is seen in the first 3 months of life, puberty and a gradual increase is also noted between ages 40–65 years, especially in women. AP in adolescent boys may be 2–5 times greater than normal adults and correlates with bone growth [(16)]. Likewise, African Americans have a 10–15% higher serum AP and smokers may have up to 10% higher AP compared to nonsmokers. Finally, individuals with Blood type O and B may have elevated AP following a fatty meal due to influx of intestinal AP. Some of the hepatic and extrahepatic causes of elevated and low AP are shown in Tables 2, 3 and 4.

Evaluation of Cholestasis

The first step in evaluating a patient with an elevated AP level is to try and identify the source of the AP. This can be done by either fractionation of isoenzymes by electrophoresis or obtaining 5'nucleotidase and gamma glutamyl transpeptidase (GGT) levels both of which are elevated in hepatobiliary disease [(17)]. The next step is to determine whether cholestasis is secondary to intrahepatic or extrahepatic disease process. Cholestasis is considered intrahepatic when impairment in bile excretion occurs at the hepatocellular level and extrahepatic cholestasis refers to large bile duct involvement, either due to an intrinsic process or secondary to extrinsic compression [(18)]. However, certain conditions like primary sclerosing cholangitis (PSC) may involve both intrahepatic and extrahepatic bile ducts [(19)].

History and Physical

A comprehensive history and physical examination is essential and may provide important clues that help with diagnosis. A history of painless jaundice with or without a palpable mass, strongly favors malignant biliary obstruction [(20)]. Choledocholithiasis on the other hand frequently presents with abdominal pain and jaundice [(21)]. Life threatening complications such as acute ascending cholangitis may occur in patients with common bile duct stones mandating urgent intervention. Cholangitis may occur due to partial or complete biliary obstruction and may present with the classic triad of fever with chills, right upper quadrant pain and jaundice [(21)]. A history of previous biliary surgery and biliary manipulations increases the possibility of cholangitis in a patient with jaundice [(22)]. History should also include details regarding alcohol consumption, recreational drug use and medications including recently discontinued medications, herbal and over the counter medications. The clinical setting in which cholestasis occurs should be considered. For example, cholestasis in a severely ill patient is likely secondary to sepsis [(23)]. Finally, a family history of cholestatic liver disease may suggest a hereditary disorder [(24)].

The two most common symptoms suggestive of intrahepatic cholestasis include pruritus and fatigue. These symptoms however, are nonspecific and may be observed in extrahepatic

cholestasis and other liver diseases such as viral and alcoholic hepatitis [25]. Pruritus can be severe leading to impairment in quality of life. Scratching can result in skin mutilation and severe refractory itching maybe an indication for liver transplant [26]. Pruritus in infants usually manifests as irritability and failure to thrive; while older children may experience poor school performance, sleep impairment and attention deficits [27]. The mechanism of pruritus in liver disease is not entirely understood, and may be related to retention of bile salts or endogenous opioids [28]. Fatigue is an intriguing but poorly recognized symptom in patients with chronic cholestatic liver disease. Fatigue can be very disabling, particularly in patients with primary biliary cirrhosis (PBC) [29].

Hypercholesterolemia is a common feature of intahepatic cholestasis [28]. The abnormal lipotrotein observed in patients with cholestasis is lipoprotein X, which has low atherogenic potential [31]. Clinically, lipid abnormalities may present with xanthomas (cholesterol deposition in tendon sheaths, bony prominences like elbow and knee, buttocks and peripheral nerves) and/or xanthelasmas (cholesterol deposits in the periorbital skin folds [32]. Occasionally, xanthomas may develop in acute extrahepatic biliary obstruction, and are usually the eruptive type. Surgical removal of xanthelasmas is usually not effective and recurrence is typical. Malabsorption of fat soluble Vitamin E, D, K, A, is common. Careful attention to prevent and treat these vitamin deficiencies plays an important role in the treatment of chronic cholestatic diseases [33]. Osteopenia and osteoporosis are seen in approximately 10–50% of patients with chronic cholestatic liver disease [34].

Investigation

Laboratory investigation should include complete blood count with differential, liver enzymes (aminotransferase enzymes and AP) GGT, liver synthetic function (albumin, bilirubin, prothrombin time), viral serologies, autoantibodies antinuclear antibody (ANA), smooth muscle antibody (SMA), anti mitochondrial antibody (AMA), pronuclear anti-neutrophil cytoplasmic antibody (p-ANCA) and immunoglobulin levels.

Transcutaneous abdominal ultrasound (TUS) is usually the first imaging modality to evaluate for intra and extrahepatic biliary dilatation [35]. TUS is a noninvasive and relatively inexpensive test with a high degree of specificity to identify bile duct obstruction [36]. However, TUS maybe technically difficult in obese patients and the pancreas is often difficult to image with the technique; furthermore, approximately 60 % of common bile duct (CBD) stones maybe missed by TUS. A CT scan is comparable to TUS in detection of stones and provides additional information regarding the liver parenchyma and may help identification of mass lesions, for example, a pancreatic tumor. CT scan is however not very helpful in delineating the biliary tree [37]. A negative TUS and CT in a patient strongly suspected to have extrahepatic obstruction should be followed by further imaging. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) are safe and accurate options for detection of lesions causing extrahepatic obstruction [38]. The gold standard for visualizing the biliary tract is endoscopic cholangiopancreatography (ERCP). ERCP can identify the cause and level of obstruction; in addition, brushings and biopsy may be obtained and therapeutic interventions such as stone extraction, dilatation of biliary strictures and if required stent placement can be undertaken [39]. Percutaneous transhepatic cholangiography may be required in patients with altered anatomy, such as a history of prior surgery such a gastrectomy or a choledochojejunostomy.

Once extrahepatic cholestasis is excluded, further workup of intrahepatic cholestasis is warranted. Certain autoantibodies are highly specific; a positive antimitochondrial antibody (AMA) is highly suggestive of PBC [40]. The diagnostic criteria for PBC include an elevated AP, positive AMA and characteristic liver biopsy features, although liver biopsy is no longer

considered essential for the diagnosis of PBC [41]. Liver histology consistent with PBC in a patient with biochemical tests suggestive of PBC but a serologic pattern suggestive of autoimmune hepatitis (positive ANA or ASMA) is classified as autoimmune cholangiopathy [42]. However, low titers of ANA and SMA may be seen in a number of conditions including PBC, PSC and other cholestatic diseases [43]. In the absence of a positive AMA, MRCP is indicated to exclude PSC. The characteristic features of PSC include diffuse multifocal stricturing and dilatation involving the intrahepatic and/or extrahepatic ducts [44]. In an appropriate clinical setting, an abnormal cholangiogram similar to PSC may indicate AIDS cholangiopathy or other secondary cholangitis [45]. When diagnosis is unclear and/or for staging purpose, a percutaneous liver biopsy is indicated. The liver biopsy specimen should contain at least 10 portal tracts for accurate diagnosis. An algorithm for evaluating the adult patient with cholestasis is presented in Fig. 1.

Genetic disorders of cholestasis

A number of genetic disorders characterized by defects in the hepatocellular transport system have been described. These include, among others, progressive familial intrahepatic cholestasis (PFIC), benign recurrent intrahepatic cholestasis (BRIC), cystic fibrosis and Dubin–Johnson syndrome (Table 5).

PFIC refers to a heterogeneous group of autosomal recessive cholestatic liver diseases which often present in the neonatal period or first year of life. Without a liver transplant, death from liver failure may occur in the first decade [24]. Three types of PFIC have been described and the inheritance pattern of all three forms is autosomal recessive. The phenotypic findings of PFIC1 (Byler Disease) and PFIC2 (Byler syndrome) are similar. PFIC1 is due to a mutation in *FIC1* (Familial intrahepatic cholestasis 1) located on chromosome 18q 21–22, whereas PFIC2 is due to mutation in the *BSEP* gene located on chromosome 2q 24 [46, 47]. These children present with severe cholestasis, pruritus, elevated bile acids and interestingly a normal serum GGT level [48]. PFIC2 patients usually have higher serum aminotransferase levels and are at an increased risk for development of hepatocellular carcinoma which may occur in the first or second decade of life [49]. PFIC1 patients may demonstrate extrahepatic features such as watery diarrhea, bile acid malabsorption, pancreatitis and nephrolithiasis. PFIC 3 involves mutations in the *ABCB4* gene, the gene that encodes multidrug resistance protein 3 (MDR3) [50]. PFIC3 is characterized by markedly elevated serum GGT and usually present in later infancy or early childhood [48]. Liver failure can occur in childhood or adulthood in people with PFIC3 [50]. Obligate *MDR3* heterozygous women have an increased risk for developing cholestasis during the 3rd trimester of pregnancy [51].

Benign recurrent intrahepatic cholestasis (BRIC) is a rare autosomal recessive or sporadic liver disease characterized by intermittent episodes of cholestasis. Two types of BRIC have been described. BRIC1 is due to mutations in *FIC1* and BRIC2 due to *BSEP* mutation. This condition follows a benign course, with no progression to chronic liver disease [52, 53]. During a cholestatic episode, both the serum bilirubin and AP are elevated, while GGT remains normal. Symptom free periods may last several weeks to months.

Other rare geneteic cholestatic conditions include Dubin-Johnson syndrome, a rare benign autosomal recessive, relapsing disorder caused by a *MRP2* mutation [54]. This condition is characterized by conjugated hyperbilirubinemia and an elevated GGT level. Cystic transmembrane regulator (*CFTR*) mutations results in impairment in chloride secretion and cholestasis [55]. Finally, Alagille's syndrome (due to a mutation in *JAG1*) is a rare condition characterized by hypoplasia of the intrahepatic bile ducts and other developmental defects [56].

Primary Biliary Cirrhosis or Chronic Nonsuppurative Destructive Cholangitis

The exact etiology of PBC is not known; however it is believed that PBC develops when a genetically susceptible individual is exposed to an environmental trigger [57]. Evidence that genetic factors play a major role is based on high concordance rate of 63% in monozygotic twins versus 0% in dizygotic twins and 5–6% of patients have a first degree relative with PBC [58]. A link between PBC and HLA-DR8 and HLA-DPB1 and other genetic variants of HLA class II suggest an inherited immune system abnormality resulting in inability to suppress the inflammatory injury contributing to biliary cell lysis observed in PBC [59]. Xenobiotics (drugs, pesticides, cosmetics) and certain infections (Chlamydia pneumoniae, Escherichia coli, Retrovirus, Novosphingobium aromaticivorans, Lactobacilli) are thought to play a role in the pathogenesis of PBC by either possibly triggering an autoimmune reaction or by causing a direct toxic effect [60, 61]. Smoking is a possible risk factor for the development of PBC and possibly accelerates progression [62].

Clinical features

PBC is more common among women, with female: male ratio of 10: 1[62]. Nearly 60 % are asymptomatic at the time of diagnosis and are incidentally detected to have an elevated serum AP level [63]. Fatigue and pruritus are common symptoms and may be present in 40% to 80% of patients; although these symptoms do not correlate with the severity of liver disease [29, 64]. Fat-soluble vitamin deficiencies (vitamins A, D, E, and K) and osteoporosis on the other hand are usually seen in patients with advanced PBC [34, 65].

Diagnosis

PBC is characterized by a cholestatic pattern of liver enzyme abnormalities with a predominant elevation of serum AP and GGT. An elevated serum bilirubin is an independent predictor of survival [66]. However, the hallmark of PBC is presence of AMA which is positive in 90–95% of patients with a sensitivity of 98% and specificity 96 %[40]. ANA may be present in 20–50% of patients with PBC [68]. The role of imaging in PBC is mainly to exclude possible biliary obstruction, cirrhosis and screen for hepatocellular carcinoma in patients with advanced PBC and cirrhosis. The characteristic histology in PBC is the “florid duct lesion” with involvement of interlobular bile ducts, inflammation and bile duct injury. The infiltrate comprises of plasma cells, macrophages and eosinophils. Noncaseating granulomas may be present [69]. Occasionally the only finding on histology maybe ductopenia defined as absence of bile ducts in greater than 50% of portal tracts (Fig 2).

Treatment

Ursodeoxycholic acid (UDCA) is the only FDA-approved drug for PBC and is used at a dose 13–15mg/kg/day. UDCA improves liver tests including serum bilirubin and other serum biochemical markers as well as liver histology [70]. When used in early stages of PBC, UDCA halts progression of disease. Individuals with a favorable biochemical response have a significantly reduced likelihood of needing a liver transplant and reduced mortality from decompensated liver disease [71]. Liver transplantation is reserved for patients with decompensated PBC. Liver transplant does not change the AMA positive status even though only 20% have recurrence of PBC at 5 years post transplant [72].

Autoimmune Cholangiopathy (AIC)

AIC is the term used to describe the 5% to 8% of AMA-negative PBC patients. AIC is characterized by a cholestatic liver enzymes pattern, liver histology consistent with PBC and

a negative AMA [73]. Hypergammaglobinemia and positive ANA and SMA may be present. AIC is treated similarly to PBC and may represent a single disease with a variable autoantibody profile. The autoantibodies found in autoimmune cholestatic conditions are shown in Table 6.

Primary Sclerosing Cholangitis (PSC)

PSC is a chronic cholestatic liver disease characterized by concentric and obliterative fibrosis of the intrahepatic and/or extrahepatic bile ducts which may progress to biliary cirrhosis [74]. Although the first case of PSC was most likely described in 1929 in a patient with ulcerative colitis who developed cirrhosis, it was only in 1960 that the term “primary sclerosing cholangitis” was coined [75]. PSC is frequently associated with inflammatory bowel disease (IBD), commonly ulcerative colitis (UC) [76]. Approximately 62–73% of patients with PSC have UC and 3–4% of UC patients develop PSC. Interestingly, even though IBD is more frequent in women, PSC has a 2:1 male predominance [77]. The median age of onset is about 40 years and it is more common among non-smokers compared to smokers [78].

PSC is a multifactorial disease. Environmental factors and genetic predisposition likely plays a role as siblings of patients with PSC have a prevalence of 1.5%; approximately a 100 fold increased risk [79] The major histocompatibility complex (MHC) encodes human leukocyte antigen (HLA) class I and class II molecules and MHC class I chain-like alpha-molecules (MICA). MICA has a role in the innate immune response as ligands for natural killer cells. Polymorphisms in MICA * 008 have been associated with PSC [80]. Furthermore there is an increased prevalence of HLA-B8, HLA-DR3, and HLA-DRw52a in patients with PSC; with HLA-B8 in up to 60 to 80% of PSC patients [81]. More recently, several genome wide-association studies (GWAS) have demonstrated that, outside of the HLA complex, at least 3 non-HLA susceptibility loci (chromosome 13q31, chromosome 2q35, and chromosome 3p21), all three of which are also implicated in UC, may contribute towards risk of development of PSC [82].

The association of PSC and UC, has led to considerations of both infectious and autoimmune contributions to the pathogenesis; PSC like UC, is an autoimmune disease and bacterial or viral antigens may enter the portal circulation through an inflamed colonic wall triggering an immune reaction [83–85]. The autoimmne hypothesis is further supported by the presence of autoantibodies, such as p-ANCA or ANA in PSC patients·[86]. However, unlike other autoimmune conditions, PSC has a male predominance and does not respond to corticosteroids [87].

Clinical features

PSC should be suspected in any patient with IBD presenting with cholestatic liver enzyme abnormalities. Similar to PBC, the majority of patients are asymptomatic at the time of presentation [88]. The most common symptoms at presentation include intermittent episodes of fatigue, pruritus, and/or abdominal discomfort. During the initial course of the disease, most symptoms resolve spontaneously [89]. The serum AP and bilirubn may also fluctuate, indicating transient biliary obstruction from biliary sludge or stones. Episodes of fever, chills and jaundice may reflect bacterial cholangitis from biliary obstruction rather than advanced disease. Persistent jaundice suggests advanced PSC and should raise the suspicion of cholangiocarcinoma (CCA).

Diagnosis

ERCP has traditionally been the gold standard for the diagnosis of PSC; however MRCP is increasingly being used a noninvasive alternative to ERCP [90]. ERCP should currently be

reserved for situations where an intervention such as dilatation and stenting of biliary stricture is anticipated or if MRCP technique is sub-optimal for diagnosis. ERCP is also indicated if a dominant stricture is present to obtain cytologic brushings to rule out CCA [91]. On cholangiography, the strictures are short and alternate with dilated segments producing characteristic 'beaded' appearance [92]. The chatacteristic histologic finding in PSC is "onion skin" fibrosis pattern present in 7–50% [93].(Fig 2). This describes the periductal concentric fibrosis that occurs around the interlobular and septal bile ducts, resulting in ductpenia and bile duct proliferation. The classical PSC finding of obliterative fibrous cholangitis which represents concentric fibrosis with obliterative cholangitis is present in less than 10% patients with PSC[93]. Conditions that result in secondary sclerosing cholangits should be ruled out prior to making a diagnosis of PSC. These include intraductal stones, ischemic cholangiopathy, bile duct injury from intra-arterial chemotherapy, AIDS cholangiopathy, recurrent pyogenic cholangitis and bile duct injury during surgery [94].

Patients with PSC are at risk for development of a number of malignancies. PSC patients have a 5–10% life time risk for developing CCA [95]. Risk factors for CCA include older age at time of diagnosis of PSC, longer duration of IBD, smoking and alcohol use and patients who have undergone proctocolectomy [95]. An annual MRI/MRCP or ultrasound along with CA19-9 is recommended for screening for CCA [96]. PSC patients also have increased prevalence of gallbladder cancer, colorectal cancer or dysplasia and hepatocellular cancer [97]. Therefore an annual colonoscopy with multiple biopsy is recommended for screening purposes [98].

Treatment

UDCA has been evaluated for the treatment of PSC [99]. Results from studies using low dose UDCA were inconclusive and a high dose (28–30mg/kg/day) trial was discontinued early because of development of serious adverse events including cirrhosis, death or liver transplant [100]. UDCA at a dose up to 13–15 mg/kg per day, may show improvement in some features of cholestasis, but does not have survival benefit or delay in need for transplant [101]. As a result, UDCA is not recommended for the treatment of PSC [102].

IgG4-related sclerosing cholangitis (IgG4-SC)

'IgG4-related sclerosing disease' is a systemic inflammatory condition characterized by IgG4-positive plasma cells and T-lymphocyte infiltration frequently involving multiple organs [103]. The tissues commonly involved include the pancreas, bile duct, gall bladder, kidney, retroperitoneum, and salivary glands [104]. IgG4-related sclerosing cholangitis (IgG4-SC) is a variant of this condition characterized by bile duct involvement [105]. IgG4-SC is associated with autoimmune pancreatitis (AIP) in 80–90% of patients [105].

Clinical Features

IgG4-SC clinically and cholangiographically resembles PSC. It is however important to differenciate the two conditions as IgG4-SC is responsive to steroid therapy [106]. Table 7 outlines some of the differences between the two conditions.

Diagnosis

IgG4-SC is relatively easy to diagnose when associated with AIP. AIP manifests with typical radiologic features such as "sausage-like diffuse pancreatic swelling with peripancreatic capsule-like rim, and irregular narrowing of the pancreatic duct" along with an elevated serum IgG4 level [107]. Ghazale et al have shown that in AIP, an IgG4 over 140mg/dl had a sensitivity and specificity of 76% and 93% respectively, and when the cutoff

was raised to 280mg/dl, the sensitivity and specificity was 53% and 99% respectively [108]. However, 9% of patients with PSC may also have elevated IgG4 levels. IgG4-SC patients may be associated with hypergammaglobulinemia, positive ANA in 40–50%, positive rheumatoid factor in about 20% and eosinophilia in 15% [108]

The cholangiographic features in IgG4-SC is classified into 4 types [109]

Type 1 Stenosis occurs in the lower part of the common bile duct; often misdiagnosed as pancreatic cancer

Type 2 Diffuse stenosis involving intrahepatic and extrahepatic bile ducts; closely resembles PSC.

Type 3 Stenosis involving the hilar region and the lower part of the common bile duct; often misdiagnosed as CCA

Type 4 Stenosis only in the hilar hepatic region; often misdiagnosed as CCA.

The gold standard for the diagnosis of IgG4-SC is histology showing the characteristic diffuse lymphoplasmacytic infiltration, infiltration by $IgG4^+$ plasma cells and obliterative phlebitis which is distinct from the ductopenia and periductal concentric fibrosis seen in PSC[111] (Fig 2).

Treatment

This disease may be characterized by spontaneous relapsing and remitting course, but is very responsive to corticosteroid therapy and steroids can induce remission [111]. There is no concensus regarding dose and duration of steroid therapy, but an initial high dose of prednisone 40mgs/day for 3–4 weeks followed by a tapering course guided by biochemical and radiological response should be considered [93]. Steroid sparing immunosuppressive therapy with azathioprine and mycophenolate mofetil and rituximab maybe sometimes indicated for patients with a relapsing course requiring chronic immunosuppressive therapy [112].

Hepatic Sarcoidosis

Sarcoidosis is a multisystemic disease of unknown etiology characterized by the presence of non-caseating granulomata [113]. Sarcoidosis primarily affects the lungs and lymph nodes but can involve almost every organ including the liver [114]. Hepatic sarcoid usually affects individuals between 20–40years of age; African-Americans have a two to three fold increased risk of developing sarcoidosis compared to Caucasians [115]. African-Americans also may have a more chronic and severe form of disease [115].

Clinical Features

Most patients with hepatic sarcoid are asymptomatic and only 5–30% present with symptoms such as nausea, vomiting, abdominal pain, fever with night sweats, myalgia and possible weight loss [116]. Approximately 50–80% of patients with systemic sarcoidosis have hepatic involvement [117].

Diagnosis

The most common biochemical abnormality noted in hepatic sarcoid is an elevated AP and GGT and the extent of elevation may reflect severity of fibrosis [118]. Serum Angiotensin-converting enzyme (ACE) level is almost always elevated in hepatic sarcoid and is associated with an active disease process[118]. Other granulomatous conditions have not been associated with significant ACE level elevation [119]. Hepatic nodules are usually diffuse, multiple and small, usually approximately 1.0 cm in diameter [120]. On CT imaging,

these nodules generally appear as multiple low –attenuating, non-conteast enhancing lesions and on MRI they appear as hypodense lesions on T2 weighed sequence without contrast enhancement[120,121]. The main histological features in hepatic sarcoid are noncaseating granulomas which consist of multinucleated giant cells (Fig 2). Granulomas are typically in the portal and periportal areas [122]. In more advanced cases, chronic cholestasis, ductopenia and cirrhosis may be evident [122].A number of other conditions may be associated with granulomas including PBC, lymphoma, tuberculosis among others [123].

Treatment

Corticosteroids is the main stay of treatment for hepatic sarcoidosis[124].There is general consensus that treatment is not required in the absence of symptoms or biochemical abnormalities. In patients with symptoms such as fever and abdominal pain, low dose prednisone 10–15mg/day is often associated with clinical response [125]. Steroid therapy also appear to improve liver tests in those with mild to moderate enzyme elevation [124]. However, biochemical response does not correlate with histologic response and progression to cirrhosis may occur [124]. In advanced hepatic sarcoiosis, steroids are unlikely to have any significant benefit [126]. Methotrexate, hydroxychloroquine, azathioprine, and cyclophosphamide have been used as steroid sparing agents and have been shown to be of some benefit [126]. UDCA has also been to be useful in patients with chronic cholestasis and may improve clinical and biochemical abnormalities [127].

Portal hypetension (PHT) is a rare complication of hepatic sarcoid and warrants mention. PHT may occur with or without cirrhosis [128]. In the absence of cirrhosis, PHT may be a result of obstruction of portal flow by granulomas, arteriovenous shunts that increase portal blood flow, granulomatous phlebitis causing portal and hepatic vein occlusion resulting in ischemia and/or extrinsic hepatic vein obstruction by granulomas resulting in Budd –Chiari syndrome [128,129]. Liver transplantation may be the ultimate treatment option in these patients [130].

Parenteral nutrition – associated liver disease (PNALD)

Parenteral nutrition (PN) induced hepatobiliary disturbance is more common in children, particularly premature infants compared to adults [131]. This condition should be suspected in patients on PN who develop hyperbilirubinemia and liver enzyme elevation after rulling our drug induced liver injury, sepsis and extrahepatic obstruction. Liver enzyme elevation is usually observed within 1–4 weeks after initiation of PN and in most instances improves in spite of continued PN [132]. Two patterns of injury maybe seen with PNALD: steatosis and steatohepatitis or cholestasis [133]. Steatosis is more common in adults while cholestasis occurs in children [133]. PNALD range from mild liver enzyme elevation with resolution following cessation of PN, to steatosis and steatohepatitis, cholestasis and in a few patients may progress to severe hepatobiliary damage and cirrhosis [134]

The etiology of PNALD is multifactorial. Decreased gallbladder emptying resulting in cholelithiasis, bacterial overgrowth due to the unused gut leading to gut translocation of endotoxins into the portal circulation and/or amino acids in PN solution are all thought to contribute to the development of PNALD [133–135]. Immaturity of the biliary secretory system plays a major role in the development of cholestasis in premature infants [136]

PNALD can be prevented by early resumption of oral or enteral intake, prevention of hypoxia, prompt treatment of sepsis, treating hypoproteinemia and avoidance of hepatotoxic drugs. Using a cyclic PN schedule and decreasing excess amino acids in PN will also likely prevent liver injury [137].

Treatment

Treatment options for PNALD are limited. UDCA has been shown to be possibly effective in PNALD [138]. Bowel decontamination with antibiotics such as metronidazole may be helpful [139]. Intestinal transplantation, frequently along with liver transplantation, is reserved for patients with short bowel syndrome dependent on PN who develop overt or pending liver failure or other life threatening complications from PN [140].

Intrahepatic Cholestasis Of Pregnancy (ICP)

ICP is defined as pruritus and elevated serum bile acid levels in otherwise healthy pregnant women [141]. ICP usually manifests around 25 to 32 weeks of gestation, resolves following delivery and tends to recur in approximately 45%–70% of subsequent pregnancies [142].

Clinical Features

The main manifestation of ICP is pruritus which affects all parts of the body and is frequently worse at night. Occasionally patients may present with steatorrhea [143]. Jaundice occurs in less than 25% of patients [144]. Hormonal factors (both estrogen and progesterone), genetic and environmental factors likely influence the development of ICP [145]. *MDR3* mutations account for approximately 15% of cases of ICP [146].

Diagnosis

The diagnosis of ICP is one of exclusion and all other causes of hepatic impairment should be considered first. Prompt resolution of symptoms following delivery favors a diagnosis of ICP. Serum AP will be elevated but is of limited diagnostic value in pregnancy. Aminotransferase enzyme elevation is usually mild to moderate and patients may infrequently have hyperbilirubinemia although serum bilirubin level usually less than 5 mg/dL [147]. Serum bile acid (BA) level is a more sensitive and specific biochemical marker of ICP, both for diagnosis and subsequent monitoring [148] Specifically, serum cholic acid level is increased resulting in an increased cholic/chenodeoxycholic acid ratio; this is the most sensitive test for diagnosis of ICP [149]

Treatment

UDCA is the treatment of choice for ICP and has been shown to not only control symptoms, but also reduce both serum bilirubin and BA in maternal and cord blood [150]. More importantly, no maternal or fetal adverse effects have been noted [150]. Dexamethasone is occasionally used but is less effective compared to UDCA [151].

Cholestasis Related to Sepsis

Sepsis is the most common etiology of jaundice and cholestasis in the ICU setting [152]. Cholestatic jaundice may complicate both gram positive and gram negative bacteremia, E.coli being the commonest organism linked to this condition [153]. This syndrome accounts for a third of neonatal jaundice [152]. Sepsis induced liver disease may be a primary hepatic dysfunction which occurs immediately following shock as a consequence of hypotension and/or hypoxia and is manifested by significant elevation in aminotransferase enzymes. Secondary hepatic dysfunction occurs due to Kupffer cell activation by bacteria and endotoxins and release of inflammatory mediators [154].

Intrahepatic cholestasis related to sepsis is characterized by disproportionate elevation in serum bilirubin compared to serum AP. Serum AP is usually 2–3 times above the upper limit of normal. Serum aminotransferases are usually less than 2 times the upper limit of normal [155]. Biliary obstruction and hetabobiliary infection should be ruled out prior to

making a diagnosis of sepsis related cholestasis. Unlike other cholestatic conditions, pruritus is not a major manifestation of cholestasis associated with sepsis. Histologically, bile is seen in bile canaliculi and hepatocytes. Hyperplasia of Kupffer cells and apoptotoc bodies may be present on histology [152].

Aggressive supportive measures and treatment of underlying infection are the mainstay of treatment of cholestasis of sepsis. At present there are insufficient data regarding regarding the use of UDCA in the treatment of sepsis related cholestasis [156].

Drug Induced Liver Disease (DILI)

DILI is probably the most common cause of cholestatic liver disease and accounts for 40% of adults presenting with hepatitis [157]. Hepatoxocity can occur following use of prescription drugs, over the counter medications, toxins and herbal medications and accounts for about 10% of all adverse drug reaction [158]. DILI may manifest as pure cholestasis due to an abnormality in canalicular bile flow or a mixed hepatocellular cholestatic pattern [159]. The pathogenesis of drug-induced liver injury is poorly understood. In genetically susceptible individuals, a direct injury triggered by a drug or its metabolites may initiate both an innate and adaptive immune response [160]. Certain drugs also directly bind to intracellular proteins or inhibit mitochondrial function resulting in decreased energy production and eventually, activation of apoptotic pathways resulting in programmed cell death [161]. In a subset of patients, inhibition of hepatobiliary transporter systems by a drug may be a major factor in pathogenesis of cholestasis. Studies support the role of mutations in the *ABCB11* and *ABCB4* genes encoding BSEP and MDR3 in DILI [162]. Drugs that affect canalicular membrane transport pumps such as MDR3 also can interrupt bile flow causing cholestasis.

Clinical Features

DILI may present with nonspecific symptoms such as abdominal pain, nausea and fatigue or as an acute illness with jaundice[163]. Chronic drug-induced cholestasis may present with pruritus. DILI often resolves following withdrawal of the offending drug but occasionally can cause significant bile duct damage and chronic liver disease [163]. Table 8 outlines some of the manifestations of DILI. DILI should be suspected in individuals with no known medical illness who present with symptoms and abnormal liver tests shortly after initiation of a medication, with prompt improvement following withdrawal of the drug.

Diagnosis

It may not always be possible to establish a temporal relationship between drug exposure and clinical presentation. When a single agent is involved, diagnosis may be relatively simple but most individuals are on multiple medications with potential for hepatotoxicity. Furthermore, other liver conditions such as autoimmune hepatitis or nonalcoholic steatohepatitis may have a similar clinical presentation. A detailed history including the duration, dose, route of administration, prior exposure to drug, use of over-the counter medications and herbal medications should be obtained. Laboratory studies to assess degree of liver enzyme elevation and synthetic liver function should be performed. A liver biopsy remains an important tool for the diagnosis although it is not always necessary[164] (Fig 2).

Treatment

Treatment of DILI is early recognition and withdrawal of the offending drug. Specific treatment is limited to acetaminophen and valproic acid overdose which are treated with specific antidotes N-acetylcysteine and L-carnitine respectively [165]. In individuals with a predominant cholestatic pattern, ursodeoxycholic acid has been used [166]. It is important to

remember that acute liver failure in this setting has a mortality rate of over 80% without liver transplant and should prompt an early transplant referral.

Extrahepatic Cholestasis

Choledocholithiasis and Acute Ascending Cholangitis

Cholelithiasis affects approximately 10% of adults in the United States, and 10–20% of patients with symptomatic choleithiasis have concomitant choledocholithiasis [167]. A CBD stone may result in biliary obstruction and bile stasis resulting in the life threatening complication of acute ascending cholangitis. Biliary manipulation during ERCP is the second most common cause of acute cholangitis [168].

Clinical Features—Choledocholithaisis may be asymptomatic and one-third of patients may have normal laboratory values [169]. Symptomatic stones can present with RUQ pain, fever and jaundice. This triad of symptoms is present in approximately 55–70% of patients with acute cholangitis [170]. The pentad which includes hypotension and altered mental status is seen in less than 5–7%.

Diagnosis—90% of patients with obstruction from stones will have an elevated AP and GGT [170]. Bile cultures are positive in 80% to 100% of patients who have cholangitis, and blood cultures may be positive in 20% to 70% [171]. TUS remains the initial screening test for CBD stones with a sensitivity and specificity of 25–60% and 95–100% respectively [172]. MRCP has evolved into an accurate noninvasive modality for diagnosis of CBD stones with sensitivity and specificity comparable to ERCP (85% and 93% vs 93–98% and 97–100% respectively) [173]. MRCP however may be falsely negative in patients with stones smaller than 6mm. Endoscopic ultrasound (EUS) is also comparable to ERCP for detection of stones and does not carry the risk of pancreatitis and cholngitis [173]. The main advantage of ERCP over MRCP is that ERCP is both a diagnostic tool but can be used for therapeutic interventions such as stone retrieval [169].

Choledochal cyst

This is a rare condition characterized by cystic dilatation of intrahepatic ducts, extrahepatic ducts or both [174]. This condition is more common among Asians compared to Caucasians with a female preponderance (F: M is 4:1) [174] Reflux of pancreatic secretion into CBD results in damage to bile ducts and recurrent cholangitis, pancreatitis, chronic inflammation and fibrosis [175].

Clinical Features—Most patients are diagnosed in childhood and the classic triad of abdominal pain, jaundice, and a palpable right upper quadrant abdominal mass is seen in only 10–20% of adults [176].

Diagnosis—No specific laboratory tests help in the diagnosis. TUS is the initial test of choice, although MRI and MRCP is preferred as they delineate the biliary tree, define the extent of involvement of bile ducts and also provide information on surrounding parenchyma [177]. On MRCP, choledochal cysts appear as a markedly dilated CBD with saccular formation. On histology, the cyst wall appears thin and fibrous and adults may have evidence of biliary cirrhosis [178]. The most dreaded complication of choledochal cyst is CCA which occurs in approximately 20% of adults and therefore surgical resection is recommended for the treatment of choledochal cysts, except Type 3 (choledochocele) which carries a low risk of CCA [179,180].

Benign And Malignant Biliary Stricture

Benign biliary stricture may occur in patients with previous history of surgery resulting in bile duct injury, history of PSC, recurrent choledocholithiasis, chronic pancreatitis, and history of blunt trauma to the abdomen and following liver transplant. In approximately 30% of patients the injury to bile ducts during surgery is unrecognized and patients may present many years later with biliary strictures [181]. Anastomotic strictures following liver transplant usually occur about 2–6 months following surgery [182]. Chronic pancreatitis accounts for 9–10% of benign strictures which occur in the intrapancreatic section of the CBD [183].

Pancreatic cancer is the commonest cause of malignant biliary stricture [184]. Other conditions that cause malignant stricture include CCA, Gall Bladder tumor and ampullary tumor. CCA or biliary tree cancers can involve the intrahepatic or extrahepatic ducts. Klatskin tumors are CCA that occurs at the bifurcation of the right and left main bile ducts or proximal hepatic ducts [185]. Malignant strictures can be due to either a primary bile duct cancer causing narrowing within the bile ducts or extrinsic compression by a tumor in an adjacent organ such as the head of the pancreas.

Clinical Features—Benign strictures maybe asymptomatic, although cholangitis is a common presentation. Patients with pancreatic cancer usually present with painless jaundice. Jaundice is also the commonest symptoms in patients with CCA. Decreased appetite, weight loss and epigastric pain radiating to the back should raise a suspicion of a malignant process.

Diagnosis—Extrahepatic cholestasis presents with elevated AP and GGT with normal or near normal aminotransferase enzymes. Hyperbilrubinemia may be significant in patients with pancreatic cancer with serum bilirubin often higher than 20mg/dl [186]. A serum CA19-9 above 100U/ml has a sensitivity and specificity of 75% and 80% respectively for CCA in patients with PSC [186]. As discussed earlier, workup for extrahepatic obstruction includes imaging such as TUS or CT, followed by MRCP or ERCP depending on the clinical situation and need for possibly therapeutic interventions. When malignancy is suspected, brushings during ERCP of biliary tree for cytology should be obtained. Advanced techniques such as digital image analysis (DIA) and fluorescence ***in situ*** hybridization (FISH) have greatly increased sensitivity and specificity for detection of CCA [187].

Management of Cholestasis

Pruritus—This is a challenging clinical problem which often complicates chronic cholestatic liver disease. Cholestyramine is the first line agent in patients with moderate pruritus and the recommended dose is 4–16gm per day in divided doses [188]. Cholestyramine is a resin that binds to bile salts in the small intestine thereby interrupting enterohepatic circulation and decreasing its reabsorption by approximately 90% [188]. Cholestyramine however is unpalatable and interferes with absorption of other drugs such as digoxin, warfarin and thiazides [189]. Rifampin has also been shown to be useful in the treatment of pruritus. Rifampin decreases hepatic uptake and facilitates renal elimination of bile acids [190]. The recommended dose is 300–600mg/day. Liver tests should be monitored closely while on rifampin as severe hepatitis may sometimes occur [191]. There have been a few small studies that report benefit with Phenobarbital; however it is less effective compared to rifampin and cholestyramine and is therefore not recommended for treatment of pruritus [192]. The antidepressants sertraline and paroxetine have been shown to be useful in a few trials [193,194]. Increased opioidergic neurotransmission in the brain may have a role in the pathogenesis of pruritus. Opiod receptor antagonist naloxone, nalmefene and naltrexone have been shown to cause substantial relief of symptoms [191]. The main drawback for their

use however is the potential for opiod withdrawal [195]. The role of UDCA has been discussed above under specific cholestatic diseases. Plasmapheresis should be reserved for patients with refractory disabling pruritus when all other treatment options are ineffective [196]. Finally, liver transplantation is an indication for severe pruritus secondary to cholestatic liver disease [197].

Fatigue—No therapy has been found to be effective in the treatment of fatigue. UDCA has not been shown to be useful and fatigue may persist even after liver transplant, although its intensity may be reduced [198,199]. CNS stimulants such as modafinil and low dose amitryptyline may be beneficial in some patients [200].

Osteoporosis—Calcium and Vitamin D should be recommended to all patients with chronic cholestatic liver disease in order to prevent metabolic bone disease. Once osteoporosis is established, bisphosphonates are recommended. In a study comparing etidronate and alendronate, the latter was found to be more effective in increasing bone mass [201].

Fat soluble vitamin deficiencies—All patients with chronic cholestatic liver disease should have annual vitamin A, D, E, K levels monitored and appropriate treatment should be initiated if found to be deficient.

Hyperlipidemia—The utility of cholestyramine for the treatment of hyperlipidemia in this group of patients has not been established. UDCA has been shown to significantly reduce total cholesterol, VLDL and LDL cholesterol but has no effect on triglyceride or HDL cholesterol, and the maximum benefit was seen in patients with higher baseline cholesterol and higher serum bilirubin values [202]. Clofibrate, due to an unknown mechanism, results in paradoxical increase in cholesterol in patients with PBC and therefore should not be used for the treatment of hyperlipidemia in these patients [203]. Statins have been shown to be effective in reducing cholesterol with frequent monitoring of liver enzymes and should possibly be avoided in patients with severe cholestatic disease [204].Plasmapheresis is reserved for patients with very high serum cholesterol ; approximately 6gms of cholesterol can be removed by a single plasma exchange resulting in decrease in serum cholesterol levels, resorption of xanthomata, decrease in of the pain caused by xanthomatous neuropathy and also improvement in pruritusassociated with cholestasis [205].

Outcome in the Representative Case: The patient was started on prednisone 40mgs once a day, which was slowly tapered based on his clinical response. He achieved complete biochemical response within 3–4 months of therapy. The patient is currently on a maintenance dose of 10mg/day per day and his APU/L is 90, ALT 31mg/dl and AST 35mg/dl.

Conclusion: Although the causes of cholestasis are numerous, a systematic step by step work up starting with a comprehensive history and physical and complemented by laboratory testing and appropriate imaging, results in an accurate diagnosis in almost all patients.

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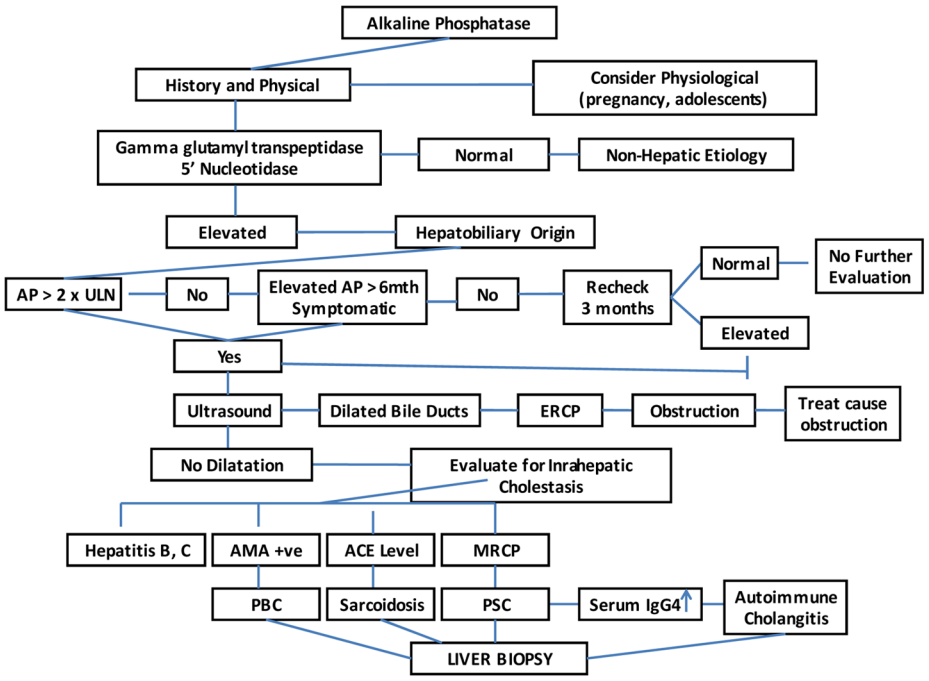

Fig 1.
Propose algorithm for work up of elevated alkaline phosphatase

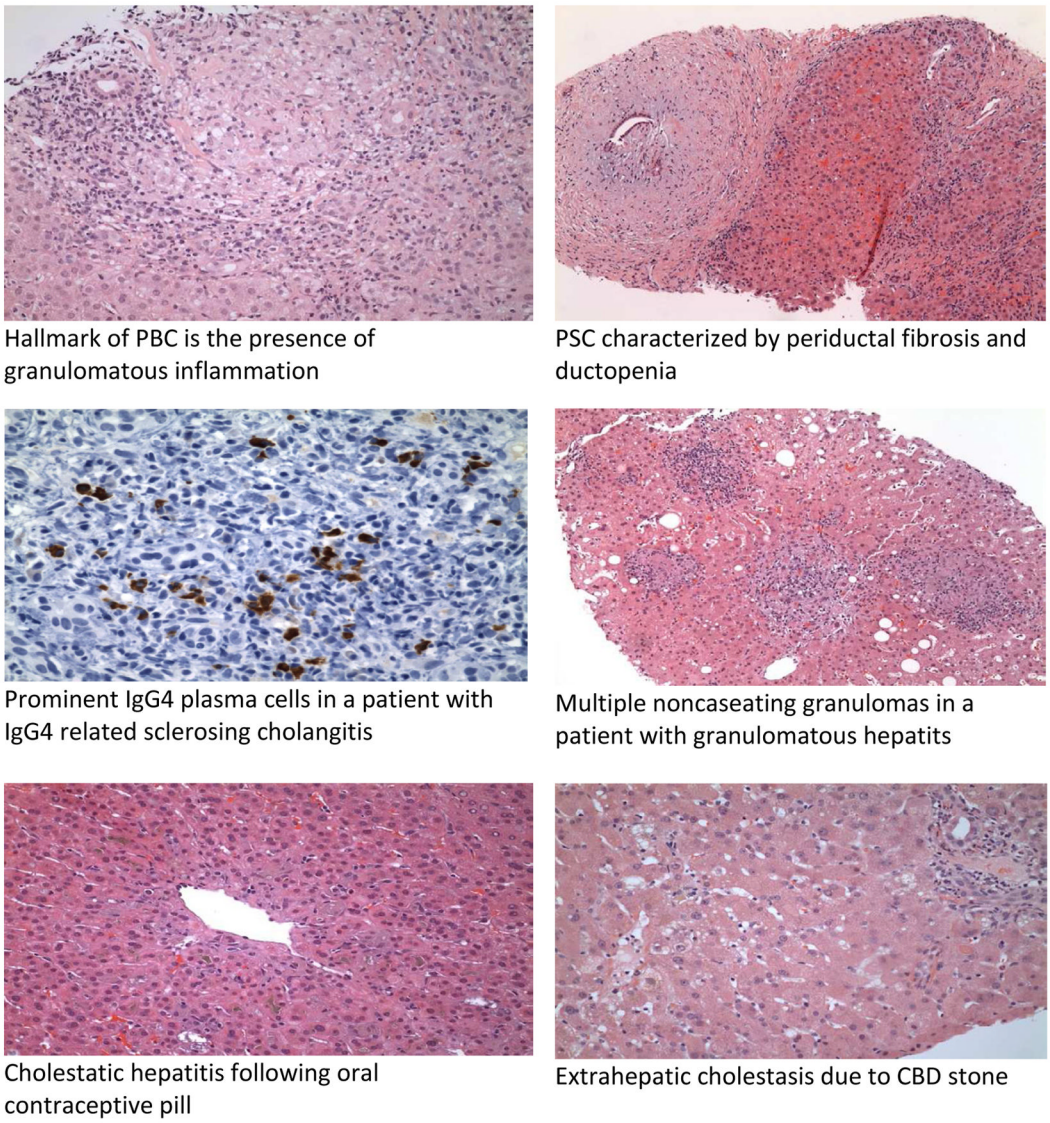

Fig 2.
Histological features in cholestatic liver disease

Table 1

Categories based on liver tests

Test	Liver Disease Category			
	Hepatocellular	Cholestatic	Infiltrative	Mixed
ALT/AST	++	N/+	N/+	++
AP	N/+	++	+/++	++
TB	N/+ to ++	N/+ to ++	N/+	N/+ to ++

ALT – alanine aminotransferase; AST – aspartate aminotransferase; AP – alkaline phosphatase; TB – total bilirubin, N – normal; + to ++ - degree of elevation

Table 2

Non-hepatic cause of elevated alkaline phosphatase

Physiological	Pregnancy Adolescence Following a fatty meal in subjects with blood group O or B
Bone disease	Healing Fracture Paget's Disease Osteomalacia Vitamin D insufficiency Rickets Malignancy: osteogenic sarcoma, metastatic
Renal	Renal Failure
Heart	Heart Failure
Endocrine	Hyperthyroid Hyperparathyroid
Malignancy	Lymphoma Leukemia Renal cell carcinoma Multiple endocrine neoplasia (MEN) II

Table 3

Causes of Cholestatic Liver Disease

INTRAHEPATIC CHOLESTASIS	EXTRAHEPATIC CHOLESTASIS
Hepatitis: Viral (B,C), Alcoholic	Extrinsic Obstruction
Genetic:	- stones
- Benign recurrent intrahepatic cholestasis	Malignancy
- Progressive familial intrahepatic cholestasis	- Pancreas
- Dubin-Johnson, Rotor's Syndrome	- Gall bladder
- Drugs and hebal remedies	- Metastatic
Pregnancy	- Cholangiocarcinoma
PBC	- Ampullary cancer
PSC	Pancreatitis
Granulomatous liver disease	Pancreatic pseudocyst
- Infections	Parasitic Infection
- Sarcoidosis	Secondary sclerosis (surgery, chemotherapy)
Infiltrative:	
- Amyloidosis	
- Lymphoma	
Idiopathic Adult Ductopenia	
Autoimmune Cholangitis (PSC-like)	
Autoimmune Cholangiopathy (PBC-like)	
Prolonged TPN	
Postoperative state	
Sepsis	
Malignancy	
- Hepatocellular	
- Metastatic	

Table 4

Low Alkaline Phosphatse

Malnutrition
Wilsons Disease
Hypothyoidism
Zinc deficiency
Vitamin C deficiency
Low phosphorus level
Pernicious anemia

Table 5

Hereditary Cholestatic Syndromes

Protein/Gene	Chromosome	Clinical disease state	Lab findings	Characteristic Features
FIC1/ATP8B1	18q21	PFIC1	GGT low Serum bile acids increased	AR; severe pruritus; cholestasis; diarrhea; ductular proliferation absent
		BRIC1	GGT low	Periodic attacks of cholestasis
BSEP/ABCB11	2q24	PFIC2	GGT low Serum bile acids increased	AR; severe pruritus; cholestasis; ductular proliferation absent
		BRIC2	GGT low	Periodic attacks of cholestasis
		ICP	GGT low or high	Cholestasis, pruritus in 3rd trimester of pregnancy
MDR3/ABCB4	7q21	PFIC3	GGT increased Bile acids normal	AR; moderate pruritus; cholestasis
		ICP		
MRP2/ABCC2	10q24	Dubin Johnson	Conjugated hyperbilirubinemia	Jaundice
CFTR/ABCC7	7q31	Cystic fibrosis		Associated PSC

Table 6

Autoimmune Antibodies in Cholestatic Liver Disease

	PBC	AIC	PSC	IgG4-SC
ANA	20–50%	79–100%	7–77%	43–80%
SMA	20%	50%	15–20%	< 5%
AMA	95%	0	0	0
p-ANCA	3–33%	unknown	80%	<5%
Ig	IgM	IgG	IgG, IgM	IgG

PBC –primary biliary cirrhosis; AIC- autoimmune cholangiopathy; PSC – primary sclerosing cholangitis; IgG4-SC – IgG4 relates sclerosing cholangitis; ANA – anti nuclear antibody; SMA – smooth muscle antibody; p-ANCA perinuclear anti-neutrophilic cytoplasmic antibody; Ig - immunoglobulin

Table 7

Differences Between PSC and IgG4-SC

	PSC	**IgG4-SC**
Age	25–45yrs	65yrs
Male Gender	65%	80%
Association with IBD	Present	Absent
Other organ involvement	No	Pancreas frequently involved
p-ANCA	Positive	Less common
Elevated serum IgG4	7–9%	70%
Histology	Ductopenia Periductal concentric fibrosis	Abundant IgG4 + plasma cells Periportal fibroinflammatory nodules
Cholangiogram	Multifocal “beaded”; pruned tree appearance of intrahepatic and extrahepatic ducts	Segmental, long strictures with prestenotic dilatation, distal CBD involvement, pancreatic duct involvement
Response to Steroid	No	Yes

PSC –primary sclerosing cholangitis; IgG4-SC – IgG4 related sclerosing cholangitis

Table 8

Clinical Characteristics of Drug Induced Liver Injury

Subclinical	Granulomatous hepatitis
ALT < 3 x ULN	Noncaseating granulomas
Usually benign	Usually asymptomatic
Resolves weeks to months after stopping drug	Hepatocellular or cholestatic pattern
Eg – Sulfonamide, Salicylate	Eg - Allopurinol, Carbamazepine, Cephalexin
Acute Liver Injury	Chronic Hepatic Injury
Acute hepatitis – resembles viral hepatitis	Chronic hepatitis – resembles autoimmne hepatitis
Cytotoxic hepatocelluar injury	Extrahepatic features common
High mortality if acute liver failure develops	(arthralgia, eosinophilia, rash)
Eg - Acetaminophen	Eg. Methydopa, Diclofenac
Cholestatic Injury – resembles extrahepatic	Chronic Steatosis
May take months for jaundice to improve	Usually macrovesicular
Eg - Amoxicillin-clavulanate	Eg - Valproate, Amiodarone
Mixed	Cirrhosis
Increased risk of chronic liver disease	Eg - Methotrexate, Azathioprine, OCP
Eg - Phenytoin	
Acute Steatosis	Phospholipodosis
Usually microvesicular	High incidence of cirrhosis
Eg - Amiodarone, Zidovudine, Herbal remedies	Eg - Amiodarone, Chloroquine
Chronic Cholestasis	Vascular Disease
Chronic intrahepatic –resembles PBC	Hepatic vein thrombosis :
Ususally resolves after stopping drug.	Thrombosis of hepatic vein or inferior vena cava
Eg - Amitriptyline, Ampicillin, Chlorpromazine	Eg - OCP
Vanishing bile duct syndrome	Sinusoidal obstruction syndrome (SOS)
Ductopenia	Clinically resemble Budd-chiari
C progress cirrhosis	Eg - Azathioprine, Vitamin A
Eg -Amoxicillin, Clindamycin, Carbamazepine	Peliosis hepatis:
Biliary sclerosis - resembles PSC	Multiple, small, blood filled cavities in hepatic parenchyma
Eg - Intra-arterial infusion 5-flurodexoyuridine	Eg- Anabolic steroids, arsenic