Acute Viral Hepatitis- Beyond A, B and C*

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As defined by Neil Theise at the 9th edition of Robbins (1), "Hepatitis" stands for histologic patterns of lesions found in the livers infected by hepatotropic viruses , by other viruses leading to a liver inflammation in the context of systemic infection, or due to autoimmune , drug or toxins involving the liver.

Pathological findings encompasses a set of diffuse necro-inflammation of the liver, presenting heterogeneous distribution. In acute hepatitis , necro-inflammation is more intense in the parenchyma, whereas in chronic forms the inflammation is more relevant at the portal tract and at the porto-parenchymal interface (acinar zone 1).

The present review is based on our recent comprehensive approach to acute viral hepatitis at Saxena´s Practical Hepatic Pathology (2). Herein , we will target especially the histological patterns of injury in acute viral hepatitis, describing aspects related to :

1. The so-called "hepatotropic viruses A, B, C, D and E" ;

2. Viruses responsible for the "icteric hemorrhagic fevers" (dengue, hantavirus, yellow fever).

A brief mention to viruses causing hepatitis in immunosuppressed patients will also be presented.

Although globalization has exposed travelers to previously unexpected agents, potentially disseminating viruses from different regions of the world, remarkable differences in incidence of each type of viral hepatitis still remain . A recent series of 206 cases of acute viral hepatitis from India [3] identified HEV in 95 cases, HAV in 36, HBV in 18 and mixed infections of these viruses in additional 27 cases. HCV was detected in only one patient. The other 29 cases were ascribed to CMV or EBV. In the USA, official reports of acute hepatitis from CDC for the year 2013 include 1,781 cases of HAV, decreasing to 1,239 in 2014. Notifications of acute hepatitis due to HBV were 3,050 in 2013 and 2,791 in 2014. Acute hepatitis due to HCV totalized 2,138 in 2013, rising to 2,194 in 2014. No data regarding HEV is depicted and, elsewhere in the site, CDC comments that, in the USA, HEV is believed to be uncommon . When symptomatic hepatitis E does occur, it is usually the result of travel to a developing country where hepatitis E is endemic. [4]

Acute liver failure (ALF) may result from viral hepatitis. In 2014, the CDC reported 76 cases of deaths in the US ascribed to HAV [4] . Deaths due to acute hepatitis B were reported in 13 cases. However, chronic Hepatitis B was considered the cause of death of 1,843 patients. The CDC report did not mention death due to Acute Hepatitis C, but Chronic Hepatitis C was considered the cause of death of 19,659 patients [4]

Although not mentioned at the CDC report [4] , in other countries acute liver failure is mentioned in 0.1% to 4.0% of patients infected with hepatitis E, with a predilection for pregnant women, 30% of whom may develop acute liver failure.[5]

PATTERNS OF LESIONS IN ACUTE VIRAL HEPATITIS

Lobular parenchymal lesions are predominant, with variable number of swollen/ballooned hepatocytes. Small foci of lymphocytes, macrophages and plasma cells, even in early infection, surround damaged hepatocytes or fragments of dead hepatocytes, a lesion known as *lytic necrosis* or *spotty necrosis* .[6] Individual hepatocytic death due to apoptosis may also be numerous, known as *acidophilic bodies* and *Councilman-Rocha Lima bodies*. Cellular remnants phagocyted by Kupffer cells may be seen as iron deposits on Perls stain, useful hints for the diagnosis of resolving acute hepatitis when H&E aspects are bland. Portal edema and variable amounts of mononuclear infiltrate are usually less impressive than parenchymal lesions. Bile duct injury is usually mild, although acute hepatitis E may show variable degrees of cholangitis[7]. Mild cholestasis may be seen in acute hepatitis, with bile pigment found in the cytoplasm of hepatocytes or in biliary canaliculi. Although more relevant biliary changes may be seen , especially in elder patients, this finding should require the differential diagnosis with drug-induced injury or, exceptionally, even with bile duct obstruction.

Hepatocytes at the interface with portal tract are usually not damaged, although in Hepatitis A, lymphocytes spill over the limiting plate. Since portal fibrosis and neoangiogenesis are not features of acute hepatitis, when patterns of both acute and chronic hepatitis coexist, the pathologist must consider the possibility of an acute viral infection occurring in an already inflamed liver. An important example for such finding is hepatitis D virus (HDV) superinfection of livers chronically infected by HBV.[8]

In most cases of acute hepatitis, especially those due to hepatitis A and E, the loss of individual hepatocytes due to apoptosis and spotty necrosis do not disturb trabecular architecture and, once viral infection resolves, usually within 2 – 4 months after infection, regeneration from neighboring adult hepatocytes leads to complete restoration of structure and function of the liver.

In some cases of acute viral hepatitis, groups of hepatocytes die, resulting in collapse of reticulin framework, known as *confluent necrosis*.[6,9] When confluent necrosis links centrilobular venules to the neighboring ones, a "vascular bridge" ensues ("central-central bridging" or "central-portal bridging"). Boyer and Klatskin suggested that confluent necrosis linking central veins to portal tracts might lead to a presinusoidal-postsinusoidal shunt,[10] with a high risk of evolution to cirrhosis. This debate is still open for further studies especially assessing the liver microvasculature.

An infrequent clinical condition resulting from acute viral hepatitis is "fulminant hepatitis," with liver failure occurring few weeks after the onset of acute hepatitis. In this setting, confluent necrosis may become very extensive , leading to *submassive* or even *massive necrosis*. Due to the

irregular distribution of necrosis, histologic features from needle liver biopsies do not predict clinical outcome in such instances[11]

Extensive necrosis may be mistaken with fibrosis; the distinction can be aided by silver impregnation stains such as the Gomori silver stain. Confluent necrosis leads to approximation of reticulin fibers (collagen III fibers) due to parenchymal collapse, whereas chronic active fibrogenesis leads to deposition of both collagen III and collagen I fibers. Collagen III appears as narrow black fibrils (reticulin fibrils), whereas collagen I bands appear brown . Chronic fibrogenesis is accompanied by production of elastic fibers,visualized by the Shikata orcein, van Gieson, or Weigert stain, whereas acute collapse lack elastic fibers.[12]

Liver regeneration, in most cases with predominance apoptosis and spotty necrosis, is based on neighboring mature hepatocytes, completely restoring lobular architecture. In early biopsies, this appear as a widening of liver cell trabeculae , with "double cell plates" of hepatocytes (sometimes binucleated , or multinucleated) or appearing as "pseudoacinar" .When regeneration from adult hepatocytes is not effective, activation of a common progenitor epithelial cell of the liver, purported to be located in the canals of Hering at periportal regions, may lead to a network of small tubular-canalicular structures reminiscent of biliary ductules positive for CK19. These are embedded in variable amounts of collagen and may lead to a fibrous scar as in cases of submassive/massive hepatic necrosis[13]

The fate of liver microarchitecture after acute hepatitis depends on the etiologic agent as well as the patterns of necrosis and regeneration. Hepatic structure and function are usually completely restored in a few months in cases where parenchymal damage consisted only of apoptosis or spotty necrosis, whereas variable degrees of fibrous scars may develop in cases with more extensive confluent or submassive/massive necrosis, even after resolution of the infection.

Histologic Hints to the Causative Virus

Nowadays, the etiological diagnosis of acute hepatitis is achieved by serology, with sensitive tests detecting viral antigens in Hepatitis B or antibodies to viral proteins in Hepatitis A, C, D and E. Molecular tests, most of them based on Polymerase Chain Reaction (PCR), are also important for the diagnosis of ongoing infection by these viruses and also for other agents in icteric hemorrhagic syndromes and in viruses infecting immunocompromised patients. Although most histologic patterns are common to all types of acute hepatitis, some features are more frequently associated with specific viruses.

Hepatitis A

Lobular features are usually predominant, with spotty necrosis and many apoptotic bodies. Interestingly, the portal infiltrate may be impressive, with plasma cells and lymphocytes, frequently “spilling over” into the limiting plate. Information of serological positivity for HAV is important for the differential diagnosis with chronic interface hepatitis, especially in cases with prolonged or

relapsing disease, which may last for more than 6 months. Minor cholestasis may be seen in these cases.[14]

Hepatitis E

Hepatitis E infection is endemic in the India, sub-Saharan Africa, and Mexico, where infection is waterborne. More recently, food-born zoonotic disease or blood-born infections have been published in the United States, France, Japan and England.[15,16]

HEV genotypes 1 and 2 infect only humans and cause mainly waterborne outbreaks, whereas genotypes 3 and 4 are widely represented in the animal kingdom and are transmitted as a zoonosis mainly via contaminated meat[17,18] .Since genotype 3 has been found in most cases from industrialized countries, whereas genotype 1 prevails in India, African countries and Mexico, infection from travelling seems not to be the main source for these several series of HEV infections.

Histologically, acute hepatitis E is usually a benign, lobular hepatitis with apoptosis and spotty necrosis of hepatocytes. Bile pigment accumulation has been reported in hepatocytes and bile canaliculi and lipofuscin may be found in hypertrophic Kupffer cells. A rather peculiar finding is mixed inflammation consisting of several polymorphonuclear cells and lymphocytes. However, in a 11 cases from France, marked necroinflammatory activity was found in 9 patients and confluent necrosis in 5, leading to death in 3 patients[15]. Characteristic pathologic signs of acute hepatitis E included severe intralobular necrosis, polymorphonuclear inflammation, and acute cholangitis with numerous neutrophils.

Recently, Drebber et al found HEV RNA sequences by RT-PCR in 7 out of 221 formalin-fixed paraffin embedded liver biopsy samples with acute hepatitis of obscure etiology from Germany [7] . Histological findings were those of acute hepatitis with cholestatic features and in some cases confluent necrosis in zone 3.

Host and viral factors that determine the severity of illness caused by HEV infection are not fully understood. Viral factors, such as the HEV strain (genotype or subtype), viral load, and other coinfections, might play a role in pathogenesis. It appears that genotype 3 and 4 strains are less pathogenic in humans relative to genotypes 1 and 2. [19]

Host factors are relevant: ,Severe acute hepatitis, including cases of fulminant/submassive necrosis have been reported in pregnants and immunossupressed patients have developed chronic HEV infection progressing to cirrhosis. [19,20]

In a promising approach to the etiological diagnosis of Hepatitis E, Gupta et al[21] produced monoclonal antibodies directed to recombinant hepatitis E virus proteins codified at ORF2 and ORF3. An immunohistochemical assay tested on 30 liver biopsies collected post-mortem from the patients of ALF caused by HEV infection. yielded positive results in all paraffin-embedded samples from these 30 cases. Fifteen controls used (Five noninfected liver tissues, five HBV- and five hepatitis C virus-infected liver tissues) were all negative. If these results are reproduced in

large scale, this immunohistochemical approach may prove a valuable tool for prospective and retrospective assessment of the extent of HEV-associated problem worldwide.

Hepatitis B

Different from chronic hepatitis B, where "ground-glass hepatocytes" and "sanded nuclei," serve as important clues for etiology, acute hepatitis B does not present specific histological patterns. The absence of demonstrable viral antigens is considered to be a result of immune clearance. The lack of immunohistochemical expression of hepatitis B surface antigen or hepatitis B core antigen in acute hepatitis B has been used to differentiate it from chronic disease in asymptomatic cases with minimal lesions at biopsy.[22]

Hepatitis C

Histologic findings from acute hepatitis C in immunocompetent patients usually depicts mild lobular inflammation and relatively mild hepatocytic lesions with less ballooning and fewer apoptotic bodies than other viruses.[23]

In a series of five symptomatic cases from Johns Hopkins Hospital, two cases biopsied in the first 2 weeks, cholestasis and ductular reaction raised the differential diagnosis of early findings of biliary tract disease [24]. Two cases, biopsied at 8 weeks, showed mild to moderate lobular and portal lymphocytic inflammation without cholestasis. The only patient who had flares in hepatic enzymes after spontaneous HCV clearance, biopsied at 18 weeks, showed mild portal lymphocytic inflammation, minimal interface hepatitis, and moderate lobular lymphocytic inflammation probably reflecting evolution to chronicity. Imunohistochemical detection of HCV antigen is not sensitive enough to be useful for routine diagnosis, although the expression of HCV core protein might predict most severe relapse in post-tranplant recurrent hepatitits C [25]

OTHER VIRUSES CAUSING ACUTE HEPATITIS

Hepatitis D (Delta) Virus

HDV is an incomplete, replication-defective RNA virus that requires the molecular machinery of HBV to complete its life cycle. Thus, HDV causes acute and chronic hepatitis by coinfection or superinfection with HBV.[26,27] Replication of HDV depends on the delta antigen, which binds to viral RNA in the nucleus of infected hepatocytes by a double rolling-circle mechanism. Similar to HBV, HDV is most often transmitted by contact with contaminated blood and body fluid. [28]

In the Amazon regions of South America and in Africa, superinfection of HBV carriers with the delta virus may lead to epidemic bouts of severe acute viral hepatitis, also known as "black vomiting fever." This disease is known by different regional names such as Bangui fever in Africa, Santa Marta hepatitis in Colombia, and Labrea hepatitis in Brazil.[29,30] The disease may progress to hepatic failure and death within a few days or weeks, especially in children and young adults.[30] Thus, the clinical course of Labrea hepatitis may resemble fulminant yellow fever, with fever, jaundice, bloody vomits ("black vomits"), and finally hepatic coma and death.[27,30]

Histopathologically, beyond classical forms of submassive/massive necrosis, severe acute Delta hepatitis in Latin America and Africa shows fat and ballooning degeneration with the presence of large "spider/morula cells," preservation of canalicular structure, and scarce lymphoid infiltrate [7,29,30] However, in several cases, lack of these typical findings or overlap of morphologic criteria may make distinction from yellow fever difficult. We assessed this differential diagnosis in 42 cases of fulminant hepatic failure from the Amazon basin.[7] The most discriminating findings in Labrea hepatitis were extensive, predominantly lytic hepatocytic necrosis; portal and hepatic vein phlebitis; and "morula cells" (large hepatocytes, with large central nuclei and microvesicular steatosis) in a background of chronic liver disease. When present, reactivity for hepatitis D antigen in the nucleus of hepatocytes is pathognomonic .[7,29]

Many cases of HBV+HDV infection evolve to chronicity, with large fibrous septa, with rapid evolution to cirrhosis. Distinct from most cases of chronic HBV infection, patients who are superinfected with HDV show marked periportal and periseptal activity, even when cirrhotic . Parenchymal activity is also frequently severe, with confluent necrosis.[7,29,30]

Herpesviruses

Herpesviridae is a family of large, encapsulated, double-stranded DNA viruses encoding 100 to 200 genes encased within an icosahedral capsid. All herpesviruses are nuclear-replicating.[31] Infection by herpesviruses is highly prevalent worldwide. Usually asymptomatic, primary infection is acquired in childhood. Congenital infection may cause severe disease in multiple organs, including hepatitis. Opportunistic infection by herpesviruses is a significant cause of morbidity and mortality in immunocompromised individuals.

Epstein-Barr Virus (EBV)

EBV-related hepatitis remarkably show a dense lymphocytic inflammatory infiltrate in sinusoids and in portal tracts; the lymphoid cells are enlarged and appear atypical ("activated"), requiring differential diagnosis with a leukemic infiltrate Apoptotic hepatocytes may be seen, but the degree of cellular damage is minimal compared with the degree of inflammation. Additionally, although the lymphoid infiltrate may spill over from the portal tracts into the adjacent parenchyma, it does not destroy cells at the portal interface.[32,33]

Although etiological diagnosis rely on serological / molecular virological methods, immunohistochemistry for EBV viral capsid antigen or in situ hybridization (ISH) for EBV nucleic acids are also useful. ISH is much more sensitive, especially for detecting EBV encoded RNA (EBER) sequences, for which it is reported to be as sensitive as polymerase chain reaction (PCR).[33]

Cytomegalovirus (CMV)

Congenital CMV is frequently asymptomatic, but may lead to prematurity, various combinations of neurologic dysfunction, jaundice and hepatosplenomegaly. In the postneonatal period, primary CMV infection, especially in teenagers, presents as an infectious mononucleosis–

like syndrome, sometimes with liver dysfunction, occasionally leading to fulminant hepatic failure.[34]

Congenital CMV infection may lead to neonatal hepatitis, presenting portal and lobular inflammation, cholestasis, variable degrees of extramedullary hemopoiesis, and giant cell transformation of hepatocytes. Etiological diagnosis is favored by the finding of typical cytomegaly of bile duct epithelium, hepatocytes, and endothelial cells contain an enlarged nucleus with an inclusion that may be either eosinophilic or basophilic, surrounded by a clear halo leading to a characteristic "owl's eye" appearance. Variable numbers of basophilic granules are present in the cytoplasm of the infected cells.

Histologic findings of CMV hepatitis in immunocompetent patients are usually not pathognomonic since CMV inclusions or microabscesses are usually not found. Variable degrees of lymphocytic portal infiltrate may coexist with sinusoidal lymphocytes, similar to the histologic appearance of EBV hepatitis. Aggregates of macrophages sometimes form microgranulomas, whereas hepatocyte are only occasionally altered, with some apoptotic bodies. In immunosuppressed patients, CMV hepatitis may present as a rather mild lobular hepatitis or, less frequently, as a more severe form [35]. Microabscesses consisting of collections of neutrophils surrounding an infected hepatocyte containing a CMV inclusion are typical findings. Cytopathic effect in hepatocytes , in endothelium or in bile epithelium are almost pathognomonic, even when not surrounded by inflammation.

Immunohistochemistry (IHC) detects early-expression genes encoded protein in the nucleus of infected cells , whereas late-expression genes encode for proteins that may be found in the cytoplasm of infected cells . IHC has been considered slightly more sensitive than ISH for CMV (75.7% vs 67.6%), both claimed to be highly specific [36]

Human Herpesvirus - 6 (HHV-6)

Acute infections due to HHV-6 are frequently asymptomatic or poorly symptomatic with a spontaneous favourable outcome. Rarely, especially in immunosuppressed patients, serious clinical manifestations affect central nervous system, liver, gastrointestinal tract, lungs, and bone marrow[37]. In such instances, mainly in allograft recipients, HHV-6 may cause acute hepatitis, sometimes leading to fulminant hepatitis.

Herpes Zoster (HZV)

Although HZV almost never infects immunocompetent patients, submassive/massive hepatic necrosis may ensue in patients treated with steroids or with chemotherapy. In most of these cases, pathognomonic intranuclear herpetic inclusions are abundant. Immunohistochemistry for detection of early-expressed proteins is sensitive and specific for herpes groups. PCR detection of HZV DNA yields the most sensitive and type-specific diagnosis.[38]

Herpes Simplex Virus (HSV) Types 1 and 2

Although HSV-1 and -2 most commonly infects immunosuppressed patients, acute hepatitis and even fulminant hepatic failure may be rarely found in immunocompetent individuals [39,40]

At histology, patchy areas of coagulative necrosis with sharp borders ("punched-out necrosis" and "punctate necrosis") are surrounded by hepatocytes with enlarged nuclei with "ground-glass" intranuclear viral inclusions; syncytial multinucleated cells are frequent . Viral antigen can be demonstrated by immunohistochemistry.[41] Rare cases in pregnants or in neonates show diffuse, almost total hepatic necrosis with no viral inclusions and virtually no inflammatory response [42] Two types of viral inclusions, Cowdry A and B bodies, have been described in HSV infection . Cowdry A inclusions are small, round, and eosinophilic and are separated from the nuclear membrane by a halo. Cowdry B inclusions are large, ground-glass, eosinophilic, centrally located structures that push nuclear material to the rim of the nucleus. Type A bodies represent an early stage of nuclear infection, whereas type B bodies represent a later stage.

A recent report of a case of an immunocompetent 67-year-old male with one week of fever and abdominal pain. showing CT and MRI images compatible of liver abscesses, but with characteristic HSV histologic lesions stresses, once agin, the utility of PCR or liver biopsy with immunohistochemical detection of viral antigens or of DNA sequences by in situ hybridization for the HSV diagnosis [43,44]

Adenovirus

Adenovirus is a nonenveloped, double-stranded DNA virus that causes respiratory tract infection in infancy and early childhood. Ronan et al[45] reviewed the reports of 89 cases of hepatitis due to adenovirus, all of them immunosuppressed, only 24 (27 %) survived. Thus, although the virus rarely causes hepatitis in immunocompetent individuals, hepatitis is severe in immunocompromised hosts, progressing rapidly to acute hepatic failure if not managed urgently.

Histologically, adenoviral hepatitis consists of punched-out areas of necrosis scattered in the parenchyma. Hepatocytes at the periphery of these necrotic areas usually contain nuclear viral inclusions. These are basophilic and slightly angulated and have a "ground-glass" appearance, making the nucleus look "smudgy." Cytoplasmic aggregates of basophilic material represent viral products. Variable amounts of inflammatory cells accompany the infected hepatocytes and consist mostly of macrophages and lymphocytes. The centers of the necrotic areas may contain neutrophils or nuclear debris. Variable amounts of mononuclear portal inflammatory infiltrate and scattered granulomas may be seen. Immunohistochemistry with specific antibodies identify infected cells at the periphery of the necrotic areas.[46]

Icteric Hemorrhagic Fevers

Liver involvement by systemic infectious by non-hepatotropic viruses lead to clinical-laboratorial signs ascribable both to liver injury and to extra-hepatic manifestations [47]. High and prolonged fever, variable levels of serum transaminases, and signs of multiple organ dysfunction syndrome are the three most important clues for a systemic infection as the cause of hepatic dysfunction. Since these viruses most usually infect preferentially the endothelial cells , clinical picture also includes vascular lesions leading to petechial rash, internal bleeding and , in fatal forms, massive hemorrhage, shock and disseminated intravascular coagulation

Viral hemorrhagic Fevers (VHF) are due to enveloped RNA viruses from the families Flaviviridae, Arenaviridae, Filoviridae and Bunyaviridae, which depend on animal reservoirs - arthropods, rodents, ruminants and primates - and, so, they usually infect humans in regions where these animals live, mostly the Tropics. Human-to-human transmission or aerosol infections have occasionally been detected. [48]

Yellow Fever

The major histologic finding is hemorrhagic hepatocyte necrosis, predominantly midzonal (zone 2) . The presence of non-necrotic rings of periportal and perivenular hepatocytes in zones 1 and 3 is useful for the morphologic differential diagnosis with other causes of extensive hepatic necrosis. Numerous apoptotic bodies (Councilman-Rocha Lima bodies) are found amid this extensive hemorrhagic necrosis, especially at the borders with less-damaged hepatocytes .Macrovesicular and microvesicular steatosis are also present .[49,50] Yellow fever viral antigen is exuberant in apoptotic cells as well as in hypertrophic Kupffer cells[8]

Recent molecular tests enabled the differential diagnosis of infections caused by wild-type virus vs. the 17D vaccine strain and such approach has been useful in severe hepatitis in individuals recently vaccinated anti-YF in Brazil and in the USA [51,52].

Dengue Virus

According to WHO, Dengue virus has already infected 100 million persons, mostly in tropical and subtropical regions, transmitted by mosquitoes mainly *A. aegypti*. Potentially severe hemorrhagic forms involved 250,000 persons.[53]

Many outbreaks of Dengue infection in Latin America in the last decade led to an endemic state in several countries and even to outbreaks in Florida. During the decade 2000–2010, Brazil notified 8,440,253 cases , 221,043 (2.6%) classified as severe and 3058 fatal cases . [54]

In the USA, according to the CDC, the last reported continental dengue outbreak was in south Texas in 2005. A small dengue outbreak occurred in Hawaii in 2001 [55].

Liver involvement varies from asymptomatic elevation of aminotransferases to severe hepatitis, up to Acute Liver Failure (ALF) [53] . Apoptosis is a major mechanism of death of infected hepatocytes , thus leading to numerous Councilman-Rocha Lima Bodies in biopsies or in

autopsies. Apoptosis may be the result of combined direct viral cytopathic effect, hypoxic mitochondrial dysfunction, the immune response and accelerated endoplasmic reticular stress. [56]

Necrosis of midzonal and centrilobular hepatocytes may result from the fact that the liver cells in these areas are more sensitive to the effects of anoxia or immune response or may be a preferential target zone of the Dengue Viruses[56,57]. Although not pathognomonic, the more intense hepatocytic injury in zone 3 in Dengue is useful for the differential diagnosis with YF, which remarkably spares zone 3. Portal and lobular inflammation in Dengue is usually scarce, composed mostly of lymphocytes and macrophages

Other arboviroses – Zika and Chikungunya virus

Although , in the present days (2016) numerous cases of other arthropod-borne viruses, potentially leading to VHF, specifically zika virus and chikungunya virus are being reported from several Latin America countries and even from southern states of USA, up to now it seems that the liver has not been a major target for these agents. [58,59]

Ebola and Marburg Viruses

Person-to-person transmission led, in several African countries, to very severe outbreaks having bats as major reservoirs [60] Clinical manifestations included high fever and massive hemorrhage, shock and disseminated intravascular coagulation.

Histopathology of the liver was similar to other VHFs with hepatitis pattern without cholestasis. Main findings are hepatocellular necrosis , from spotty to confluent and minimal inflammatory infiltrate[60]. Characteristic intracytoplasmic viral inclusions are seen within hepatocytes of patients dying with EVD and, less frequently, in those infected with Marburg viruses. The viral inclusions and distribution of antigens can be confirmed by immunohistochemistry[61] . Mild to moderate microvesicular steatosis are also reported, as well as Kupffer cell hypertrophy and hyperplasia. [60]

A small number of EVD cases were diagnosed in Europe and the United States during the present outbreak, and the majority of infections were associated with travel to West Africa. [61]

Hantavirus

These rodent-borne viruses are most prevalent in Asia but that have also been found in the United States and Europe.[62,63] Febrile illness is usually followed by renal failure, but more recently multiorgan involvement with fever and pulmonary edema and hemorrhage . In our experience with necropsies in Sao Paulo, Brazil,[64] a lobular hepatitis with lymphocytes and macrophages surrounding foci of necrotic hepatocytes developed in patients who died due to severe acute edematous/hemorrhagic pulmonary lesions. These patients had a history of contact with rodents, requiring the differential diagnosis with bacterial infections such as leptospirosis. We have successfully demonstrated hantaviral antigens in endothelial cells and macrophages in many organs of Brazilian patients[64] by immunohistochemistry using an antibody developed by Zaki et al.[62]

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