



Pathology of Viral Hepatitis

Nermine A. Ehsan

Assistant Professor of Pathology

National Liver Institute

Menoufiya University

What is Viral Hepatitis?

It is the response of the patient's immune system to viral antigens displayed on cells

Which viruses?

Hepatotropic viruses

Acute Viral Hepatitis

Clinic pathological syndromes

- v **0Classic (icteric) acute type**
- v **0Subclinical anicteric**
- v **0Cholestatic**
- v **0Fulminant**
- v **0Neonatal**
- v **0Atypical variants**

Liver Response to Acute Viral Hepatitis

✓ Inflammatory cell infiltrate

○ Macrophage activity

○ Hepatocellular damage

○ Liver cell regeneration



0Inflammatory infiltrate-

0Composition

0Lymphocytes CD8, CD20

0Plasma cells

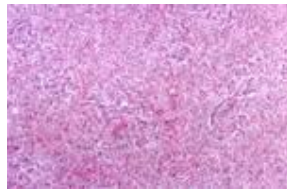
0macrophages

0Location-

0Portal tracts

0Interface

0parenchyma



Inflammatory infiltrate

0Hepatocellular damage-

00Types of necrosis

0Focal necrosis or apoptosis

fundamental lesion of acute viral hepatitis

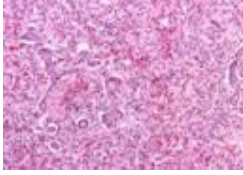
0Confluent necrosis

comprises groups of adjacent hepatocytes, often perivenular (zone 3)

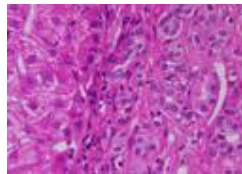
Bridging necrosis: necrosis linking vascular structures

Pan acinar: extensive necrosis involving zone 1 and 2 in addition to zone 3

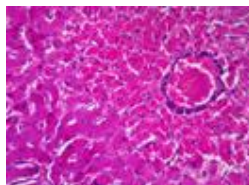
Interface hepatitis (piece-meal necrosis



Focal spotty necrosis

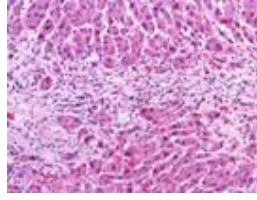


apoptosis

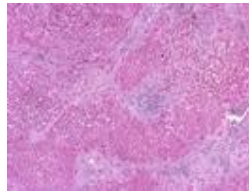


Zone 3 necrosis

Central vein with surrounding congestion and necrotic hepatocytes



Interface hepatitis



Bridging necrosis

✓ Activated Kupffer cell, circulating macrophage

expression of I CAM, ELAM, VCAM

Perl's +ve iron rich

lymphoid follicles

✓ Liver cell regeneration

distortion of cell plate

mitotic figures

liver cell rosettes

✓ Other pathological findings:

cholestasis

bile duct damage

liver fibrosis (condensation of reticulin)

0 *Evolution of the lesion-*

0 *Regression (few weeks or months*

decrease inflammation, necrosis

increase phagocytic activity

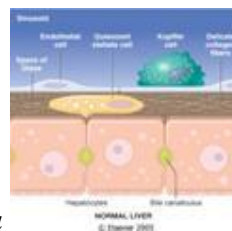
ductular proliferation

0 *Chronicity*

inflammation of the liver continues >6m

0 *Residual stage*

non specific reaction unconnected to VH



slight alteration in architecture, fibrous septa

focal liver cell regeneration

cholestasis

kupffer cell activation

0 *Differential Diagnosis of AH-*

✓ *Infectious mononucleosis (EBV) atypical lymphocytes in sinusoids*

✓ *CMV, herpes confluent necrosis, minimal inflammation*

✓ *Drugs (herbal remedies) neutrophils, eosinophils, granuloma*

, perivenular necrosis, duct damage

✓ *PBC*

✓ *AIH*

✓ *Chronic liver diseases*

Sequelae of Acute Hepatitis-

✓ Restitution to normal morphology

0 Death from severe liver damage

0 Post-hepatitic scarring

0 Viral carrier state

0 Chronic hepatitis and cirrhosis

0 Hepatocellular carcinoma

Chronic Viral hepatitis-

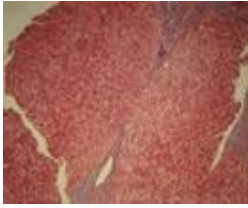
0 Definition: a pattern of clinical, biochemical and histological findings in association with one of at least three viral infection namely hepatitis B, C

0 and D viruses

✓ Clinical definition: persistent inflammation of the liver in the setting of an identifiable hepatotropic viral infection of 6 months or longer

evidenced clinically by symptoms &/or biochemical abnormalities

0Pathogenetic mechanisms-



-0Viral determinants

- ✓ 0gene products that inhibit apoptosis of infected or reacted cell population
- ✓ 0gene products that interfere with cell mediated immunity and cytokine action
- ✓ 0mutations of the virus may lead to escape from both humoral and cell mediated immunity
- ✓ 0infection of extra hepatic sites, may encourage viral persistence
- ✓ 0Direct cytotoxicity

0Pathogenetic mechanisms2-

Host Response

Humoral immune response: viral antibodies

Cell mediated immune response:

✓ 0Interferons

inhibit all phases of viral-cell interaction

induce production of host proteins (HLA-I,II, components of complement, Fc receptor)

stimulate CD8, macrophage, NK cells

✓ 0TNFalpha

Stimulate chemotaxis

Activation of macrophage, T cell

Acute phase protein transcription

IL-1

Proliferation of lymphocytes & fibroblasts

Pathological Features-

Inflammatory cell infiltration

Hepatocyte death

Hepatocyte atrophy

Hepatocyte regeneration

Hepatic fibrosis

Hepatic fibrosis-

Start by extension of portal stroma

Contains collagen I, III, reticulin, elastin produced by Hepatic Stellate Cell

Activated by: oxidant stress

lipid peroxidation products

Respond to: TGF- β , IL-1, IL-4

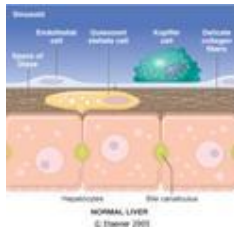
Fibrosis follows from portal tracts towards zone 1

Eventually lead to linking one portal tract to another

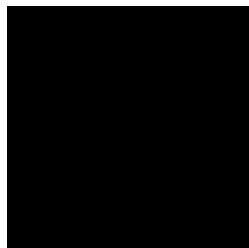
Ductular reaction starts to appear at the interface

Proliferating duct-like structures produce collagen V

(scarring)



Portal tract expansion by fibrosis



Fibrous septa, ductular proliferation

Bridging fibrosis

Fibrosis linking vascular channels, Porto-portal, Porto-central



cirrhosis

Differential Diagnosis of Chronic Viral Hepatitis- .

autoimmune hepatitis auto antibodies.

VMetabolic liver disease alpha antitrypsin deficiency1 .

WWilson's Disease copper acc fatty change Mallory bodies.

Scoring in Chronic Viral Hepatitis.

Drug induced hepatitis α methyl dopa, isoniazid, nitrofurantoin eosinophils.

v. The purpose of scoring the necroinflammatory process (HAI) was to follow the course of chronic hepatitis in asymptomatic patients Historical background

Knodell et al., 1981

Scheuer et al., 1991

Desmet et al., 1994

Batto and Ludwig 1995

Ishak et al., 1995

Metavir, 1996

Modified Knodell Ishak (et aln.-

v. Scoring the necroinflammatory activity

Interface hepatitis 0-4.

Confluent necrosis 0-6.

Focal spotty necrosis 0-4.

Portal inflammation 0-4.

Total score of 18

Modified Knodell Ishak et al.-

v. Scoring the architectural changes

No fibrosis 0 .

Fibrous expansion of some p.t. 1 .

fibrous expansion of most p.t. without septa 2 .

fibrous expansion with occasional p-p links 3 fibrous expansion with

marked bridging 4

Incomplete cirrhosis 5 .

cirrhosis 6 .

Type A Viral Hepatitis.-

√RNA hepatovirus .

.Spread by oral-faecal route .

Viral Ag:cytoplasm of Kupffer cells, hepatocytes .

Viral antibodies in serum (IgM: current infection, IgG: past infection .

Pathogenetic mechanisms: .

Hum oral immune response: B lymphocytes .

Cell mediated CD45RO (memory Tcell), NK .

Cellular cytotoxicity .

Histopathology (acute hepatitis) .

Periportal inflammation & necrosis .

Cholestatic hepatitis .

Type B Viral Hepatitis.-

√DNA hepatovirus .

√Spread by parental route mainly .

HBV antigens .

HBs

preS1: for attachment of virus to hepatocytes

preS2

X: interact with promoters of cell growth

HBc

HBe

HBV antibodies .

HBs

anti HBc

anti HBe

HBV cycle in the liver.-

vViral attachment to hepatocytes .

The virus uncoats .

Viral DNA travels to the nucleus, where it is converted to a closed circular (cc) viral DNA with the formation of viral mRNA (long, short forms)

The long form of viral mRNA serves as a template for minus strand DNA & is packaged to cytoplasm

The core particles thus formed, containing double stranded viral DNA

Assembly into complete virions

Release from the cell

Meantime, integration of segments of viral DNA into host cell genome takes place

Serological Pattern .-

vHBsAg: appear in the serum of 8 w average .

may disappear before the onset of symptoms

may persist into the symptomatic phase

may persist after symptoms abate

HBsAb: .

may persist for the entire life of patient

may decline over years & eventually disappear

HBeAg: .

IgM anti-HBcAg .

Anti-HBe: develop in acute self limiting infection .

IgG anti-HBc (hallmark of exposure or ongoing HBV infection) .

Histopathology .-

√Acute hepatitis B .

varying number of apoptotic bodies

perivenular confluent necrosis

parenchymal collapse

√Chronic hepatitis B .

interface hepatitis

lobular activity

lymphoplasmacytic infiltrate

ground glass hepatocytes (HBsAg)

√Fibrosing cholestatic hepatitis .

following orthotopic liver transplantation



Hepatitis B virus infection

Apoptotic body, ballooning degeneration, steatosis

Immunoperoxidase of HBsAg (cytoplasm of hepatocytes)

Immunoperoxidase of HBc Ag

Strongly +ve in the nucleus, some in cytoplasm of hepatocytes



Interface hepatitis, apoptotic bodies

Pathogenetic mechanisms.-

Immunological response -

Humoral immune response: antiviral antibodies

Class II pathway activation

CD4 response against HBc, HBe, HBs antigens

which help to activate CD8 B cell response

Direct cytotoxic effect

Chronic disease -

decrease CD4, CD8 in peripheral blood

weak response contribute to viral persistence

Selective immune suppression -

down regulation of viral gene expression (escape the immune response)

large viral load overwhelms the T cell response

viral mutants that escape surveillance

Hepatitis C Virus.-

√RNA virus with a lipoid envelope -

Parental spread mainly -

Acute phase is usually asymptomatic -

(some cases show fulminant hepatitis)

Chronic hepatitis: mild, incidently discovered

Histopathology of HCV.-

Microscopic picture #

scattered acidophilic bodies (apoptosis-

lymphoplasmocytic infiltrate in portal tracts, forming lymphoid aggregates and follicles-

steatosis -

bile duct damage -

confluent necrosis (zone 3-

hepatic iron stores may be increased -

hepatic fibrosis -

Pathogenetic mechanisms

√Immunological response -

CD4 proliferation & cytokine response to HCV nonstructural protein-3 correlates with viral clearance in the acute phase of the disease

Multistep CD8 responses result in viral clearance

Activation of B cell response to HCV which contribute to autoimmune effects.

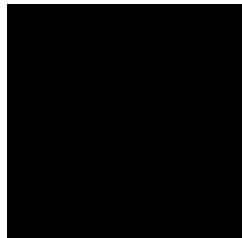
√Fibrosing cholestatic variant of chronic HCV is an example for direct cytotoxicity -

✓Established chronic disease -

HCV-specific CD4 responses compartmentalize within the liver

HCV-specific CD8 responses

Inflammatory infiltrate, apoptotic body, steatosis



Lymphoid follicle, confluent necrosis, interface hepatitis

Interface hepatitis, apoptotic body



Type D Virus Hepatitis (delta) .-

√ Negative stranded RNA

An envelope consist of HBs antigen

Parental spread

Acquired at the same time as HBV or later superimposed on a preexisting chronic HBV

Clinical syndromes:

Acute self limited

Fulminant hepatitis

Chronic hepatitis

Detection in tissue: HD Ag in nucleus

Hepatitis E Virus

√ single stranded RNA

faecal-oral route of spread

Mild disease-----fulminant

Viral particles can be found in bile ducts, hepatic sinusoidal cells, hepatocytes

Histopathology

Cholestatic: canalicular cholestasis

Gland like transformation, neutrophils

Other Hepatotropic Viruses

✓Hepatitis F virus (historical)

Double stranded DNA toga-like virus in nuclei of hepatocytes of patients with fulminant hepatitis

Hepatitis F for hepatitis of french origin

Hepatitis G virus

RNA virus, parental spread, variant of HCV

passenger virus: cause hepatitis under certain conditions

TT virus

single stranded DNA virus

post transfusion

fulminant hepatitis