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Extrahepatic manifestations of HBV

Extrahepatic manifestations of HBV

- Extrahepatic manifestations, which are thought to be mediated by *circulating immune complexes*, occur in *10 to 20* percent of patients with chronic HBV infection
- **acute hepatitis** may be heralded by a *serum sickness-like syndrome* manifested as fever, skin rashes, arthralgia, and arthritis, which usually subsides with the onset of jaundice
- The two major extrahepatic complications of chronic HBV are polyarteritis nodosa and glomerular disease.

Extrahepatic manifestations of HBV

- Upcoming clinical research, over the years, associates numerous extrahepatic manifestations during the acute and chronic episodes of hepatitis B with *significant morbidity and mortality.*
- A causal relationship between HBV and serious *autoimmune disorders* has also been observed among certain *susceptible vaccine recipients* in a defined temporal period following immunization.

Extrahepatic manifestations of HBV

- *Serum Sickness–Like Syndrome*
- *Membranous Glomerulonephritis*
- *Membranoproliferative Glomerulonephritis*
- *Immunoglobulin A Nephropathy*
- *Polyarteritis Nodosa*
- *Bullous Pemphigoid , Lichen Planus*
- *Cryoglobulinemia*
- *Guillain-Barré Syndrome*

Extrahepatic manifestations of HBV

- **Immune Complexes**
- ***Cell Mediated Immunity Against HbsAg***
- There is increasing evidence of clinical differences between ***subtypes and genotypes*** at various levels regarding extra hepatic expressions.

Extrahepatic manifestations of HBV

- As in liver disease of non-viral etiology, *these HBV related extra hepatic manifestations are nonspecific for HBV infection.*
- The variety of disorders is ***mainly based on immune complex*** reaction that includes skin rash, arthritis, arthralgia, glomerulonephritis, polyarteritis nodosa, and popular acrodermatitis etc.

Extrahepatic manifestations of HBV

- The precise ***pathogenesis*** of these extrahepatic complications has not been fully determined, although the majority represents the clinical expression of ***autoimmune*** phenomena.
- The concept is that lesions could result from the deposition of viral ***Antigen/Antibody complexes soluble in Ag excess, possibly involving HBe Ag***

Extrahepatic manifestations of HBV

- The *IgG concentration* of immune complexes have been found *greater* in patients with acute and chronic hepatitis B compared to other conditions.
- More importantly, the ***presence, composition, and concentration*** of these circulating immune complexes *correlates* with the ***clinical findings*** of rash, arthritis, and angioedema, which strongly ***suggests an etiological relationship***.

Extrahepatic manifestations of HBV

- Immunologic manifestations include circulating autoantibodies and concurrent autoimmune disorders.
- The possible *mechanisms*, include deposition of circulating immune complexes (IC's), *induction of local IC formation by viral antigens, reaction with tissue antigens by viral-induced autoantibodies or a direct viral reaction to extrahepatic tissue sites*

Transient Serum Sickness-like Syndrome

- In 10-20% of hepatitis B patients as extrahepatic manifestations are seen as transient serum-sickness like syndrome.
- Pathogenesis in the serum sickness association is with circulating immune complexes composed of HBsAg in antigen excess and anti-HBR with subsequent consumption of complement components.

Transient Serum Sickness-like Syndrome

- Symptoms usually precede the onset of jaundice by a few days to 4 weeks and subside after onset of jaundice
- Usually manifest with **fever** (<39°C), ***skin rash*** , ***polyarthritis*** (acute , symmetrical inflammation of joints of hand and knee, morning stiffness).
- No recurrent or chronic arthritis occurs after recovery.

polyarteritis nodosa (PAN)

- Most cases of polyarteritis nodosa (PAN) are ***idiopathic***, although ***HBV and HCV infection, and hairy cell leukemia*** are important in the pathogenesis of some case
- HBV accounted for ***one-third*** of the cases of PAN, but even higher prevalence rates are possible in areas with endemic HBV infection.
- HBV-related PAN has *the same clinical features as non-HBV-related PAN* and typically occurs within *four months after the onset of HBV infection*

polyarteritis nodosa (PAN)

- Patients with PAN typically present with ***systemic symptoms*** (***fatigue, weight loss, weakness, fever, arthralgias***) and ***signs*** (***skin lesions, hypertension, renal insufficiency, neurologic dysfunction, abdominal pain***) of multisystem involvement

Systemic symptoms: Fever, malaise, weight loss Neuropathy: Mononeuritis , polyneuropathy Arthralgias and/or myalgias Cutaneous Livedo reticularis, purpura, ulcers	Renal disease Elevated creatinine, hematuria, glomerulonephritis Gastrointestinal symptoms Abdominal pain, rectal bleeding New onset Hypertension Respiratory manifestations Infiltrates, nodules, cavities	Central nervous system diseaseStroke, confusion Orchitis Testicular pain, swelling Cardiac involvement Cardiomyopathy, pericarditis Peripheral vascular disease Claudication,

Renal disease

- Infection with hepatitis B virus (HBV) may be associated with a variety of renal diseases . ***The three most common types of renal disease*** resulting from HBV infection are:
- ●Membranous nephropathy
- ●Membranoproliferative glomerulonephritis (MPGN)
- ●Polyarteritis nodosa (PAN)

Renal disease

- Renal disease associated with HBV infection most commonly ***occurs in endemic areas***.
- In these areas, infection is more likely to occur during infancy and early childhood, which increases the probability of becoming a chronic carrier.
- The widespread use of hepatitis B vaccination has decreased the incidence of HBV-related MPGN, providing evidence of the probable ***pathogenetic role of HBV***

Renal disease

- Patients with HBV-related renal disease are positive for HBsAg and anti-HBc and, in those with membranous nephropathy, ***HBeAg***.
- Although some patients with HBV-related renal disease have a history of active hepatitis, a *large proportion of patients have only mild to moderate elevations in serum aminotransferases*

Renal disease

- The pathogenetic role of HBV infection has been documented primarily by the demonstration of ***hepatitis B antigen-antibody complexes in the renal lesions via immunofluorescence microscopy***, including deposition of ***HBeAg*** in membranous nephropathy. The relationship between ***HBV variants*** (eg, precore and core promoter mutations) that prevent or decrease HBeAg production and ***renal disease has not been well described***

Renal disease

- Preliminary data suggest that ***purified HBV*** can induce ***human glomerular mesangial cell proliferation*** and ***expression of type IV collagen***. In addition, ***HBV X protein*** has been shown to induce a ***proinflammatory phenotype*** in renal tubular epithelial cells, although the ***impact of increased tubulointerstitial inflammation on glomerular pathology has not been investigated***

Renal disease

- The ***diagnosis*** of HBV-associated renal disease should be suspected in patients with *acute or chronic HBV infection* who present with *clinical and/or laboratory features suggestive of glomerular disease* (eg, proteinuria and/or hematuria, acute kidney injury [AKI] or deterioration in renal function, with or without hypertension and/or edema).

Renal disease

- All patients with ***unknown HBV*** status who have evidence of nephrotic syndrome or glomerulonephritis or are found on kidney biopsy to have histologic evidence of membranous nephropathy, MPGN, or PAN, should be tested for HBsAg as part of their initial evaluation.

Renal disease

- *Confirming the etiologic role of HBV* in any of these disorders may, at times, be *difficult* since the detection of viral antigen deposition in the kidney requires techniques that may not be available in many clinical settings. In addition, the presence of viral antigens in the renal tissue may be ***coincidental rather*** than indicative of a causal relationship .

Renal disease

- ***Proof that HBV is the primary cause of the renal disease*** can only be provided by **improvement in the renal disease** with ***antiviral therapy and viral suppression***

Renal disease

- *Diagnosing HBV-associated renal disease* is ***important*** because therapy with glucocorticoids and cytotoxic agents, ***may not be beneficial*** in patients with HBV-associated renal disease and may lead to *reactivation* of *HBV replication*, hepatitis flares, and ***liver failure*** if used without antiviral therapy

Renal disease

- For most patients with HBV-associated renal disease, treatment with ***antiviral therapy alone is sufficient***. Immunosuppressive therapy with ***glucocorticoids or cytotoxic agents and plasmapheresis*** are of little benefit and are potentially harmful, ***except in***
- RPGN
- PAN and severe manifestations

Syndromes Following Hepatitis B Vaccination

- HBV vaccination may ***induce hypersensitivity and autoimmune reactions*** in susceptible individuals and healthy Subjects.
- ***Arthritis, RA, myelitis, SLE, optic neuritis, GBS, GN , MS events pancytopenia/thrombocytopenia***, reported following HBV vaccination.

Management

- HBsAg-positive patients with extrahepatic manifestations
  and ***active HBV replication may respond to antiviral therapy***

PegIFNα can ***worsen some immune-mediated extrahepatic manifestations***