HEPATIC MANIFESTATIONS OF SYSTEMIC CONNECTIVE TISSUE DISEASES

Essay

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بسم الله الرحمن الرحيم
إقرأ باسم ربك الذي
خلق ﴿١﴾ خلق الإنسان
من علق ﴿٢﴾ إقرأ وربك
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Omar Azzam

List of Contents

List of Tables

Table No.	Title	Page No.

List of Figures

List of Abbreviations

Abb.	Full term
5- AICAR	*5-amino-imidazole-4-carboxamide ribonucleotide*
5-NT	*5-nucleotidase*
6-MMP	*6-methyl mercaptopurine*
6-MP	*6-mercaptopurine*
6-TG	*6-thioguanine*
6-TIMP	*6-thio inosine-5 monophosphate*
AAD	*American Academy of Dermatologists*
ABC	*ATP-binding cassette*
ACA	*Anticentromere antibody*
ACE	*Angiotensen converting enzyme*
aCL	*Anticardiolipin antibodies*
ACPA	*Anti-citrullinated protein antibody*
ACR	*American Collegue of Rheumatology*
AIH	*Autoimmune hepatitis*
ALHS	*Acute lupus hemophagocytic syndrome*
ALP	*Alkaline phosphatase*
ALT	*Alanine aminotransferase*
AMA	*Anti mitochondrial antibodies*
ANA	*Antinuclear antibodies*
ANCA	*Antineutrophil cytoplasmic antibodies*
Anti CCP	*Anti-cyclic citrullinated peptide*
Anti LC1	*Anti liver cytosol type 1*
Anti-dsDNA	*Anti double stranded DNA*
Anti-SLA	*Anti soluble liver antigen*
Anti-Sm	*Anti smith*
Anti-topo 1	*Anti-topoisomerase 1*
AOSD	*Adult onset stills disease*
APAP	*Acetyl-p aminophenol*
APCs	*Antigen presenting cells*
aPL	*Antiphospholipid antibodies*
APS	*Anti phospholipid syndrome*
APTT	*Activated partial thromboplastin time*
ARA	*Anti RNA polymerase antibody*
AS	*Ankylosing spondylitis*
ASA	*Amino salycilic acid*
ASAS	*Assesment of Spondyloarthropathy international Society*
ASMA	*Antismooth muscle antibodies*

List of Abbreviations **(cont...)**

Abb.	Full term
AST	*Aspartate aminotransferase*
BANK1	*B-cell scaffold protein with ankyrin repeats*
BCG	*Bacillus Calmette-Guerin*
BCOADC	*Branched chain 2-oxo-acid dehydrogenase complex*
BCS	*Budd chiary syndrome*
BEC	*Biliary epithelial cells*
BMI	*Body mass index*
BP	*Blood pressure*
BUN	*Blood urea nitrogen*
C-ANCA	*Cytoplasmic or classic ANCA*
CAPS	*Catastrophic antiphospholipid syndrome*
CBC	*Complete blood count*
CI	*Confidence interval*
COPD	*Chronic obstructive pulmonary disease*
COX-2	*Cyclooxygenase-2*
CRP	*C-reactive protein*
CT	*Computed tomography*
DCSSc	*Diffuse cutaneous systemic sclerosis*
DHPCs	*Direct Healthcare Professional Communications*
DHPLs	*Dear Healthcare Professional Letters*
DILI	*Drug induced liver injury*
DMARDs	*Disease modifying anti rheumatic drugs*
ELISA	*Enzyme linked immunosorbent assay*
EMEA	*Europian Medicines Agency*
ER	*Endoplasmic reticulum*
ESR	*Erythrocyte sedimentation rate*
EULAR	*European league against rheumatism*
EUSTAR	*European scleroderma trial and research*
FDA	*Food and Drug Administration*
FFA	*Free fatty acid*
GGT	*γ-glutamyl transpeptidase*
GIT	*Gastro intestinal tract*
GN	*Glomerulonephritis*
GST-a	*Glutathione S transferase a*

List of Abbreviations **(cont...)**

Abb.	Full term
HA	*Hepatic artery*
HBsAg	*Hepatitis B surface antigen*
HBV	*Hepatitis B virus*
HCC	*Hepatocellular carcinoma*
HCQ	*Hydroxychloroquine*
HCV	*Hepatitis C virus*
HLA	*Human leukocyte antigen*
HLH	*Hemophagocytic Lymphohistiocytosis*
HSP	*Henoch-Schonlein Purpura*
HSV	*Hypersensitivity vasculitis*
HVOD	*Hepatic veno occlusive disease*
IBD	*Inflammatory bowel disease*
IFL	*Isolated fatty liver*
IIFL	*Indirect immunofluorescence*
IL	*Interleukin*
INR	*International normalized ratio*
IPHT	*Idiopathic portal hypertension*
IR	*Insulin resistance*
ITP	*Immune thrombocytopenic purpra*
IVC	*Inferior vena cava*
IVIG	*Intavenous immunoglobulins*
KCS	*Keratoconjunctivitis sicca*
KD	*Kawasaki disease*
KIR	*Killer immunoglobulin-like receptor*
LA	*Lupus anticoagulant*
LCSSc	*Limited cutaneous systemic sclerosis*
LDH	*Lactic dehydrogenase*
LFT	*Liver function test*
LKM1	*Liver kidney microsomal type1*
MAS	*Macrophage activation syndrome*
MCPs	*Metacarpo-phalangeal joints*
MCTD	*Mixed connective tissue disease*
MHC	*Major histocompatibility complex*

List of Abbreviations **(cont...)**

Abb.	Full term
MRI	*Magnetic resonance image*
MRP2	*Multidrug resistance protein 2*
MTHFR	*Methylene tetrahydrofolate reductase*
NAFLD	*Non alcoholic fatty liver disease*
NAPQI	*N-acetyl-P-benzoquinone imine*
NASH	*Non alcoholic steato hepatitis*
NAT2	*N-acetyltransferase 2*
NHL	*Non Hodgkin's lymphoma*
NK	*Natural killer*
NRH	*Nodular regenerative hyperplasia*
NSAIDs	*Nonsteroidal anti inflamatory drugs*
NYHA	*New York Heart Association*
OCP	*Oral contraceptive pills*
OGDC	*2-oxoglutarate dehydrogenase complex*
PAN	*Polyarteritis nodosa*
P-ANCA	*Perinuclear ANCA*
PBC	*Primary biliary cirrhosis*
PBMC	*Peripheral blood mononuclear cells*
PDC	*Pyruvate dehydrogenase complex*
PIIINP	*Propeptide of type III collagen*
PM	*Polymyositis*
PMN	*Polymorphonuclear neutrophils*
PSC	*Primary sclerosing cholangitis*
PT	*Prothrombin time*
RA	*Rheumatoid arthritis*
RBP4	*Retinol binding protein 4*
R-CHOP	*Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone*
RF	*Rheumatoid factor*
ROS	*Reactive oxygen species*
sIL-2Rα	*Soluble interleukin 2 receptor alpha*
SLE	*Systemic lupus erythematosis*
SLICC	*Systemic lupus international collaborating clinics*
SOS	*Sinusoidal obstruction syndrome*
SpA	*Spondylo-arthropathies*

List of Abbreviations **(cont...)**

Abb.	Full term
SS	*Sjogren syndrome*
SSc	*Systemic sclerosis*
TH0	*Uncommitted T helper lymphocyte*
TH	*T helper cell*
TLRs	*Toll like receptors*
TNF	*Tumor necrosis factor*
TPMT	*Thiopurine S-methyl transferase*
U 1 RNP	*U 1 ribonucleoprotein*
UC	*Ulcerative colitis*
UGT2B7	*Uridine diphosphate-glucuronosyl transferase-2B7*
UK	*United Kingdom*
ULN	*Upper limit normal*
WBCs	*White blood cells*
WG	*Wegener's granulomatosis*

INTRODUCTION

Hepatic involvement in different connective tissue diseases is not un common. It may present either as clinical hepatic dysfunction (jaundice, nausea, vomiting …etc) or as laboratory disturbance in liver functions specially elevated liver enzymes, alanine aminotransferase (ALT), aspartate aminotransferase (AST). Accordingly, hepatocyte metabolism integrates a vast array of differentially regulated biochemical pathways and is highly responsive to changes in portal blood composition ***(Dardevet et al., 2006).***

A variety of autoimmune rheumatic diseases including Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), Sjogren's syndrome (SS), Myositis, Vasculitis, Antiphospholipid Syndrome (APS), Behcet's syndrome and Systemic Sclerosis (SSc), have been associated with different hepatic manifestations. The pattern of liver involvement, the prevalence, significance and the specific hepatic pathology varies in each of them ***(Walker and Zurier, 2002).***

There are some reasons, direct, indirect (hepatoxicity) and fortuitous (occult viral infection and associated autoimmune or metabolic co-morbidities) for predicting a reasonable incidence of hepatic fibrosis in patients with SSc ***(Tarantino et al., 2011).***

The frequency of hepatic involvement in SLE is about 8-23 % consisting of several pathophysiological features and emerging with clinical signs including hepatomegaly (39%), splenomegaly (6%), jaundice (24%) and in 21% elevation of liver enzymes or abnormal liver histology ***(Iwai et al., 2003).***

APS is characterized by a state of Hypercoagulability potentially resulting in thrombosis in any segment of the vascular bed ***(Khamashta et al., 2004).*** Hepatic vein thrombosis i.e Budd chiary syndrome (BCS) may be the first clinical manifestation of APS with or without SLE. Therefore, this syndrome should be considered in the differential diagnosis of hepatic vein thrombosis and measurement of lupus anticoagulant (LA), anticardiolipin (aCL) antibodies (IgG and IgM) and anti b2glycoprotein1 levels should be routinely carried out in these patients ***(Espinosa et al., 2001).***

Hemophagocytic syndrome has been reported as acomplication of various connective tissue diseases, such as systemic juvenile idiopathic arthritis, adult-onset Still's diseases (AOSD), scleroderma, dermatomyositis, and SLE. Hemophagocytic syndrome developed in active SLE patients without evidences of other underlying causes of Hemophagocytic syndrome, (infections or malignancies)

has been called acute lupus hemophagocytic syndrome (ALHS) ***(Carlos-Botelho et al., 2010)***.

The occurrence of ALHS and its cytopenias was closely related to the presence of high titers of antinuclear antibodies and hypocomplementemia, indicating that the immune complex-mediated mechanisms might be responsible for the pathogenesis of ALHS. Common manifestations include high fever, pancytopenia, hepatosplenomegaly, jaundice, elevated liver enzymes, weight loss and lymphadenopathy ***(Carlos-Botelho et al., 2010).***

Safety is a common concern among rheumatologists when using non- and biologic-disease modifying anti rheumatic drugs (DMARDs) for treatment of RA. Previous randomized controlled trials have documented that methotrexate or leflunomide monotherapy may be associated with a significantly increased incidence of liver enzymes elevation: ALT and/or AST ***(Cohen et al., 2001)***. These are predominantly asymptomatic; however, persistent elevations have been shown to correlate with histopathologic changes of fibrosis assessed by liver biopsy with chronic and prolonged use of methotrexate ***(Kremer et al., 2002).***

Tumour necrosis factor-α blocking agents (anti-TNF-α agents) are used for treating conditions such as Crohn's disease, ankylosing spondylitis (AS) and RA.

Commercially available anti-TNF-α agents include etanercept, infliximab and adalimumab. Minor abnormalities in liver function tests (LFTs) results are relatively common with the use of anti-TNF-α agents. Severe hepatic reactions are much less common. These may include jaundice, hepatitis, cholestasis, autoimmune hepatitis (AIH), and acute liver failure ***(Leonardi et al., 2003).*** Infliximab is thought to contribute to development of AIH in predisposed patients by triggering development of autoantibodies these include antinuclear antibody (ANA) and anti- double stranded DNA (anti-dsDNA) ***(Eriksson et al., 2005).***

It has been estimated that the cumulative risk of developing nodular regenerative hyperplasia (NRH) when receiving purine analogues such as azathioprine for 5 years is approximately (0.5-5%) NRH is defined as a diffuse distribution of hepatocellular nodules in the absence of fibrous septae ***(Vernier-Massouille et al., 2007).***