Hepatitis C Virus Infection in Egyptian Children with Malignancy

Thesis

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Abstract:

Background: Children with cancer are at a high risk for hepatitis C virus infection due to immunosuppression secondry to chemotherapy and multiple transfusions of blood products during the course of the disease**.**

Aim: The aim of this study is to evaluate the presence of HCV infection in children with malignant diseases, different risk factors, clinical course, laboratory, histopathological findings, natural history and type of response to HCV treatment. **Methods:** The medical records of ٣١ patients recruited from the pediatric hepatology clinic at Cairo University pediatric hospital and presenting with post malignant virus C infection were reviewed retrospectively for data of medical history, physical examination and periodic evaluation clinically and laboratory during their follow up. **Results:** The mean age at diagnosis of HCV infection was ٨±٣,٣ years, the period of follow up of the patients in the hepatology clinic ranged from ٠,٣ to ١٥ years with a mean of ٢.٦± ٢,٣ years. Risk factors for HCV acquisition were chemotherapy in ٩٣,٥٪, blood transfusions in ٨٣,٩٪, operations in ٦٤,٥٪. Out of the ٣١ cases, ٥١,٦٪ were diagnosed as leukemia. At presentation serum ALT level was elevated in ٨٣,٩٪ and AST level was elevated in ٨٠,٦٪. Liver biopsy were performed to ٢٦ cases; ٩٦,١٪ had mild to moderate activity, ٣٢٪ had no fibrosis and ٦٨٪ had mild to moderate fibrosis. Eighteen cases received HCV treatment. The response to HCV treatment was ٢٧,٧٪.

Conclusion: Although hepatitis C infection acquired by childhood cancer survivors was presented initially with high rate of elevated liver enzymes and PCR positivity, it seems to have a relatively benign clinical course with mild to moderate chronic hepatitis.

Key words: HCV- Immunosuppression -Blood transfusions- Egypt- Malignancy.

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List of Abbreviations

AAP	American Academy of Pediatrics
ALCL	Anaplastic Large Cell Lymphoma
ALL	Acute Lymphoblastic Leukemia
ALT	Alanin transaminase
AML	Acute Myeloid Leukemia
anti-HCV	Hepatitis C Virus antibody
AST	Aspartate transaminase
BL	Burkitt lymphoma
BMT	Bone Marrow Transplantation
CDٔ	cluster of differentiation ٔ
CRP	C Reactive Protein
CMV	cytomegalovirus
CNS	Central Nervous System
DLBCL	Diffuse Large B Cell Lymphoma
EBV	Epstein-Barr Virus
ESR	Erythrocyte Sedimentation Rate
ELISA	Enzyme Linked Immunosorbont Assay
ETR	End-of-treatment response
EVR	End Viral Response
FDA	Food and Drug Administration
GCTs	Germ Cell Tumors
GGT	Gamma-Glutamyltransferase
HAI	Histological Activity Index
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCV-ab	Hepatitis C Virus antibody

HCV-PCR	Hepatitis C Virus- Polymerase Chain Reaction
HCC	Hepatocellular carcinoma Hepatic
HD	Hodgkin's Disease
HDV	Hepatitis D Virus
HEV	Hepatitis E Virus
HHV-٨	Human Herpes Virus ٨
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPV	Human Papilloma Viruse
HSCT	Hematopoietic Stem Cell Transplantation
HTLV-١	Human T-cell leukaemia virus type ١
IL-١b	Interleukin-١b
IRES	Internal ribosome entry site
INF	Interferon
INF-α	Interferon-α
IFN –γ	Interferon- γ
LL	lymphoblastic lymphoma
NHL	Non-Hodgkin's lymphoma
NK	Natural killer
ORF	open reading frame
PCR	Polymerase Chain Reaction
PEG-IFNα-٢b	Peginterferon -α-٢b
RBV	Ribavirin
RIBA	Recombinant Immunoblot Assay
RVR	Rapid Virological Response
SLE	Systemic Lupus Erythematosus
SVR	Sustained Virological Response
TNF-α	Tumor Necrosis Factor-α

TSGs	Tumor Suppressor Genes
UTR	Untranslated Regions
WHO	World Health Organization

Introduction:

Hepatitis C virus (HCV) was identified in ١٩٨٩ and since then significant advances have been made in understanding the molecular biology, pathology, and treatment of HCV liver disease. HCV is an enveloped, single-stranded positive-sense RNA virus, belonging to the Hepacivirus genus within the flavivirus family. The HCV genome is approximately ١٠,٠٠٠ kilobases with stereotypical genetic heterogeneity. Based on phylogenetic analysis of HCV sequences, ٦ major HCV genotypes are recognized, designated ١ to ٦, with multiple subtypes within each viral genotype **(Mohan et al., ٢٠١٠).**

Egypt has the highest prevalence of adult HCV infection in the world, averaging ١٥٪-٢٥٪ in rural communities. The main (٩٠٪) HCV genotype is type ٤. Egyptian studies documented that analysis of risk factors is significant for male circumcision by informal health care provider. Although blood transfusion, circumcision, vertical transmission, and living in a house with infected family member are the established risk factors for HCV transmission, approximately ٧٠٪ of acquired infections are due to unidentified risk factors **(El-Raziky et al., ٢٠٠٧).**

Most chronically infected children are asymptomatic and have normal or only mildly abnormal alanine aminotransferase levels. Although the natural history of HCV infection acquired in childhood seems benign in the majority of instances, the infection takes an aggressive course in a proportion of cases leading to cirrhosis and end-stage liver disease during childhood; the factors responsible for a more aggressive course are

unidentified **(Jonas, ٢٠٠٢).** An Egyptian study reported that HCV infection is not always benign in the childhood period in children and Alanin transaminase (ALT) levels remain elevated in half of the children with histological abnormalities that are detected in three quarters of HCV RNA-positive cases **(El-Raziky et al., ٢٠٠٤).**

Children who have had multiple transfusions as a result of chronic anemia, cancer or hemophilia are at a high risk for HCV and hepatitis B virus (HBV) infections. Patients who were treated for childhood cancer before HCV donor screening are a large population at a higher risk for transfusion acquired HCV infection. In countries with a high prevalence of HCV infection, exposure to such infection is a frequent problem for children with cancer **(Ansari et al., ٢٠٠٨).** A recent Egyptian study reported that a statistically significant correlation was found between HCV ribonucleic acid polymerase chain reaction (HCV-PCR) positivity (HCV viremia) and shorter inter-transfusion interval **(Ragab et al., ٢٠١٠).**

Moreover, when compared with immunocompetent patients, the immunodepression caused by chemotherapy increases the chronicity rate of viral hepatitis. The successful cloning of HCV genome and the development of serologic markers of HCV infection showed that HCV was responsible for ٨٥٪ to ٩٠٪ of parenterally transmitted non-A, non-B hepatitis. The prognosis of chronic HCV is a matter of controversy. HCV could worsen the outcome of successfully treated pediatric oncology patients because a progression rate to cirrhosis of ٢٠٪ has been documented in ٢٠-year follow-up studies in HCV-infected adults with no other disease. Furthermore, recent

studies have shown that HCV infection is a risk factor for hepatocellular carcinoma (HCC). The prevalence of HCV infection did not show any significant change in the distribution between leukemia/ lymphoma and solid-tumor patients, even if the former group had a higher exposure to risk factors for HCV infection **(Cesaro et al., ١٩٩٧).**

Patients with acute leukemia are immunosuppressed by nature of the disease and as a major side effect of the antineoplastic drugs. A recent study showed that immune reconstitution of T-cell, B-cell and Natural killer (NK) cell subsets is not gained for at least six months following therapy, and reconstitution is even more delayed in high-risk groups who receive more intensive chemotherapy **(Torben et al., ٢٠٠٥).** This immunosuppressed state increases risk of blood-borne viral infections **(Sarper et al., ٢٠٠٨).**

Older studies in pediatric cancer patients reported that, anti-HCV positive children had received significantly more blood products transfusion compared to seronegative patient **(Fink et al., ١٩٩٣).** Also, a strong relation between the volume of blood infused and the risk of HCV infection, explains the higher prevalence of HCV infection among patients tested before anti-HCV blood screening was available **(Strickland et al., ٢٠٠٠).** Moreover, an Egyptian study has reported that evidences of Hepatitis B Virus (HBV) and HCV infection were present in around half of cases with childhood malignancies and there is a significant relation between HCV (antibody and RNA) and history of transfusions. Blood and platelets transfusions were the most identifiable risk factors for acquisition of HCV and HBV **(Sharaf-Eldeen et al., ٢٠٠٧**).