Expression of Hepatocyte Paraffin 1 antibody and Vascular Endothelial Growth Factor in Hepatocellular Carcinoma and Chronic Viral Hepatitis: An Immunohistochemical study

Thesis

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ABSTRACT

The prognosis of **HCC** patients is generally very poor, that's why early detection of patients with **HCC** became attractive and beneficial.

HCC is generally well known to be extensively vascularized and the occurrence of primary intrahepatic and lung metastases suggests its mainly hematogenous dissemination. Therefore, it is possible that angiogenesis plays a pivotal role during hepatocellular carcinogenesis**.**

VEGF expression is significantly associated with a higher proliferative index and may characterize progression towards higher proliferation in hepatocarcinogenesis. Using **immunohistochemistry**, the expression of **VEGF** is much stronger in tumor cells compared with hepatocytes in normal or cirrhotic liver and high expression of VEGF, especially under hypoxic conditions was reported in liver cirrhosis and viral hepatitis infection, which both predispose individuals to hepatocarcinogenesis.

Hep Par 1 antibody has been reported to be a sensitive marker for HCC in paraffin embedded sections; its expression is confined primarily to benign and malignant hepatocytes, it was shown to be up to 90% specific for hepatocytes in histologic specimens and is useful for differentiating HCC from liver metastases.

The aim of our study is to assess the expression of hepatocyte paraffin 1**(Hep Par 1)** and vascular endothelial growth factor **(VEGF)** in liver biopsy specimens of patients having hepatocellular carcinoma compared with patients having chronic viral hepatitis **(B or C)** and liver cirrhosis to study their clinical significance as possible markers for early prediction of malignancy in chronic viral hepatitis and liver cirrhosis patients.

The study was conducted on 20 **CH**, 30 **LC,** 30 **HCC** patients and 10 **metastatic** patients considered as control. They were subjected to liver biochemical profile, viral markers, abdominal US, together with immunohistochemical studying of their liver biopsies using **VEGF** and **Hep par 1**

We concluded that **VEGF** is intense **(>75%)** in **cirrhotic** and **HCC** patients, and **chronic hepatitis patients** can be considered to be predisposed to malignancy, if they have intense expression of **VEGF**. **VEGF** expression is less intense in **liver metastases** denoting that angiogenesis may be less in liver metastases than the original tumor.

Diffuse expression of **Hep Par 1 in** chronic hepatitis and cirrhotic patients can predict their predisposition to malignancy, as most of **HCC** patients exhibit diffuse Hep par 1 expression. **Hep Par 1** plays an important role in the differentiation between **HCC** and **liver metastases** being negatively expressed in all metastatic patients.

Key words:

- **Hepatocellular carcinoma (HCC).**
- **Liver cirrhosis (LC).**
- **Chronic hepatitis (CH).**
- **Vascular endothelial growth factor (VEGF).**
- **Hepatocyte Paraffin antibody 1 (Hep par 1)**
- **Immunohistochemistry.**

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Part III: IMMUNOHISTOCHEMISTRY IN CHRONIC LIVER DISEASES:

LIST OF ABBREVIATIONS

ABC	**Avidin –Biotin complex.**
ADH3	**Alcohol dehydrogenase.**
a FGF	**Acidic fibroblast growth factor.**
AFP	**Alpha fetoprotein.**
AFU	**Alpha-1 fucosidase.**
AJCC	**The current American Joint Committee on Cancer.**
ALK-5	**Anaplastic lymphoma kinase (Ki-1).**
Ang-1	**Angiopoeitin-1.**
ANGPTL3	**Angiopoeitin like 3.**
AP	**Alkaline phosphatase(Calf intestinal).**
BAX	**BCL-2 associated X protein.**
BCLC	**Barcelona clinic liver cancer.**
b FGF	**Basic fibroblast growth factor.**
BRCA2	**Breast cancer gene 2.**
CC	**Cholangiocarcinoma.**
CLIP	**Cancer of the liver Italian program.**
CECT	**Contrast enhanced computed tomography.**
CK	**Cytokeratin.**
C-Kit	**Stem cell factor receptor.**
COX-2	**Cyclooxygenase 2.**
CTAP	**Computed tomography angio-portography.**
CTHA	**Computed tomography hepatic angiography.**
DAB	**Diaminobenzidine substrate.**
DGCP	**Des gamma carboxy prothrombin.**
DPX	**1,3-diethyl-8-phenylxanthine**
DSA	**Digital subtraction angiography.**
2D US	**Two dimension ultrasonography.**
3D US	**Three dimension ultrasonography.**
4D US	**Four dimension ultrasonography.**
EASL	**European association of study of liver diseases.**
EC	**Endothelial cell.**

ECM	**Extracellular matrix component.**
ET	**Endothelin.**
FAS	**TNF receptor superfamily member 6.**
FGF	**Fibroblast growth factor.**
FLK-1	**Fetal liver kinase1.**
FLT-1	**Fms-like tyrosine kinase receptor1.**
18F-FDG	**18 fluoro-deoxy-glucose.**
FITC	**Fluorescin Isothiocyanate.**
FNH	**Focal nodular hyperplasia.**
GADD 45	**Growth arrest and DNA damage gene.**
GPC3	**Glypican 3.**
GST-II	**Glutathione S transferase II.**
HAC	**Hepatoid adenocarcinoma.**
HAI	**Histological activity index.**
HAP	**Hepatic arterial phase.**
HBc Ag	**Hepatitis B core antigen.**
HBe Ag	**Hepatitis B e antigen.**
HBs Ag	**Hepatitis B virus surface antigen.**
HBx	**Hepatitis B x gene.**
HGF	**Hepatocyte growth factor.**
Hep par I	**Hepatocyte paraffin I.**
HLA-DR	**Human leukocyte antigen.**
hMLH1	**Human mutL homolog 1.**
HME	**Human macrophage metalloelastase.**
hMSH2	**Human mutS homolog 2.**
HPA	**Hepatocyte antigen.**
HRP	**Horse radish peroxidase enzyme.**
hTERT	**Human telomerase reverse transcriptase.**
ICAM-1	**Intercellular adhesion molecule 1.**
IEF	**Iso electric focusing.**
IGF II	**Insulin like growth factor.**
IGF II r	**Insulin like growth factor 2 receptor.**
IGF BP I	**Insulin like growth factor binding protein one.**

IGF BP 3	Insulin like growth factor binding protein three.
IHC	Immunohistochemistry.
ISH	In Situ hybridization.
IV	Intravenous.
KDR	Kinase insert domain receptor.
Ki 67	Monoclonal antibody Ki 67.
LAB	Labeled Avidin –Biotin.
LOH	Loss of heterozygosity.
MA	Metastatic adenocarcinoma.
M6P/IGF2R	Mannose 6 phosphate / IGF II receptor.
Mdm2	Transformed 3T3 cell double minute 2.
METAVIR	Meta analysis virology.
MHz	Mega hertz..
MIB1	Mind bomb homolog 1.
MMPs	Matrix metalloproteinases.
MOC 31	Mesothelioma cell 31.
MRA	Magnetic resonance angiography.
MRI	Magnetic resonance imaging.
mRNA	Messenger RNA.
MT1-MMP	Membrane type 1 matrix metalloproteinase.
MXR 7	Mitoxantrone resistance associated gene.
NCECT	Non contrast enhanced computed tomography.
NCI	Northern Cancer Institute.
NF-kB	Nuclear factor kappa B.
NO	Nitric oxide.
NS	Non Structural.
NSGCT	Non seminomatous germ cell tumors.
8-OH-dg	8 Hydroxy- 2'deoxy- guanosine.
ORF	Open reading frame.
ORFV2-VEGF	Orf virus 2 vascular endothelial growth factor.
P161 NK4	Cyclin dependent kinase inhibitor.
P21 waf1/CIP1	Cyclin kinase inhibitor protein.
PAI-1	Plasminogen activator inhibitor 1.

PBS	**Phosphate buffer solution**
PCNA	**Proliferative cell nuclear antigen.**
PDGF	**Platelet derived growth factor.**
PET	**Positron emission tomography.**
PHC	**Primary hepatocellular carcinoma.**
PIVKA	**Protein induced by vitamin K antagonism.**
PLGF	**Placental growth factor.**
PVP	**Portal venous phase.**
PVT	**Portal vein thrombosis.**
ROS	**Reactive oxygen species.**
RB	**Retinoblastoma.**
RF	**Radio frequency.**
SCT	**Spiral computed tomography.**
SERCA 1	**Sarcoplasmic endoplasmic reticulum calcium ATP ase.**
α-SMA	**Alpha smooth muscle actin.**
Src	**Kinases encoded by Rous Sarcoma virus.**
TAPA1	**Target of anti proliferative antibody 1.**
TESPA	**3-aminopropyl-trimethoxysilane**
TGF-β	**Transforming growth factor beta.**
TGF-α	**Transforming growth factor α.**
THI	**Tissue harmonic imaging.**
TIMPs	**Tissue inhibitor metalloproteinases.**
TNM	**Tumor- nodes-metastasis.**
tPA	**Tissue plasminogen activator.**
TRAP 1	**Tumor necrosis factor associated protein 1.**
TTF1	**Thyroid transcription factor 1.**
uPA	**Urokinase plasminogen activator.**
u PAR	**Urokinase plasminogen activator receptor.**
VEGF	**Vascular endothelial growth factor.**
VEGFR	**Vascular endothelial growth factor receptor.**
VPF	**Vascular permeability factor.**
XPB	**Xeroderma pigmentosum complement group B.**
XPD	**Xeroderma pigmentosum D.**

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