SUBCLINICAL HEPATOCELLULAR CARCINOMA

Edited by Tang Zhao-you

China Academic Publishers Beijing
Springer-Verlag Berlin Heidelberg New York Tokyo

Subclinical Hepatocellular Carcinoma

Edited by Tang Zhao-you

With 136 Figures and 144 Tables

China Academic Publishers Beijing

Springer-Verlag
Berlin Heidelberg New York Tokyo 1985

Tang Zhao-you, M. D.

Professor of Surgery
Chairman, Liver Cancer Research Unit
Zhong Shan Hospital
Shanghai First Medical College
Shanghai 200032
The People's Republic of China

ISBN 3-540-12664-3 Springer-Verlag Berlin Heidelberg New York Tokyo
ISBN 0-387-12664-3 Springer-Verlag New York Heidelberg Berlin Tokyo
CSBN W 14262.006 China Academic Publishers Beijing

Library of Congress Cataloging in Publication Data. Main entry under title: Subclinical hepatocellular carcinoma. Bibliography: p. Includes index. 1. Liver-Cancer. I. Tang, Zhao-you. [DNLM: 1. Liver Neoplasms. 2. Hepatoma. WI 735 S941] RC280.L5S83 1985 616.99'436 84-17887

Typesetting, printing and bookbinding: G. Appl. Wemding
2124/3140-543210

To my Teachers
To the Peoples of the World

Foreword

Hepatocellular carcinoma is a relatively rare malignancy in the Western world, but one of the most frequent fatal tumors in the Far East and in sub-Saharan Africa, that means, in the areas where the majority of mankind lives. Until a few decades ago it was mainly detected at autopsy or, far less frequently, at operation. The improvement of imaging methods and the widespread use of liver biopsy have subsequently permitted earlier recognition. Still, it has only been detected when the process was far advanced and frequently only when a palpable mass or dramatic clinical symptoms encouraged thorough clinical investigation. This detection during life led to attempts at surgical removal. Nevertheless, these often far advanced tumors were usually associated with a bad prognosis and a relatively low rate of cure or prolonged survival after operation.

Several factors are responsible for the greater clinical interest in hepatocellular carcinoma in the past decade. The reproduction of the carcinoma in experimental animals has contributed greatly to the increasing interest in the understanding of carcinogenesis in general, although the extensive experimental investigations of these animal carcinomas have had relatively little impact on the clinical management of the tumor. Advancements in surgical techniques have improved the prognosis; transplantation of the liver, however, has so far proven to be of only limited therapeutic value. Chemotherapy of hepatocellular carcinoma with various drugs and various routes of administration has also resulted in some success, though it is so far barely convincing as a widely useful therapeutic modality. The interest in hepatocellular carcinoma has been conspicuously enhanced by the recognition of its relation to hepatitis B virus infection; carriers, of which there are 200 million worldwide, are at particular risk to develop the carcinoma. Cell lines established from hepatocellular carcinoma produce some specific viral antigens, particularly the surface antigen, and integration of hepatitis B viral DNA into the genome of the host has been demonstrated in the tumor, in the surrounding liver, and in carrier livers, but the oncogenicity of the hepatitis B virus is so far not established. Nevertheless, the hope exists that elimination of hepatitis B virus infection by administration of the vaccine and/or hyperimmune globulin may prevent the tumor, thus establishing the causal relation. The relation is

also supported by the observation of hepatitis and hepatocellular carcinoma in animals infected by a virus related to, but different from, the hepatitis B virus. This holds true for the woodchuck and – especially in China – for the duck. However, factors other than hepatitis B virus infection are also incriminated in hepatocellular carcinoma. They include alcohol abuse – particularly in the Western world – and, worldwide aflatoxin, though at present it cannot be excluded that even in these instances, hepatitis B infection plays a contributory role. Other chemical agents that are potent hepatocarcinogens in animals or incriminated in tumors other than the liver seem not to cause hepatocellular carcinoma, whereas sex hormones, metabolic diseases, and the Budd-Chiari syndrome seem to be infrequent causes, and a carcinogenic role of hepatitis non-A, non-B is problematic. Hepatitis B virus infection is therefore the most common factor today in hepatocellular carcinoma, particularly in the Orient and in Africa.

Probably the most compelling reason for the rising clinical interest in hepatocellular carcinoma, however, is the discovery of more or less specific serum markers, some of them oncofetal proteins, with alpha-fetoprotein the most important in practical use today. Although moderate serum elevations may accompany unrelated diseases, for instance those referable to yolk sac disorders, otherwise conspicuous and sustained elevations have permitted screening for hepatocellular carcinoma in earlier stages even if it is not necessarily present in all cases and if some elevations are found in chronic hepatitis. While this screening takes place in many locations, the most extensive and successful such attempt has been made in China. Such screening, together with or supplemented by various imaging techniques (particularly angiography and sonography), has led to the clinical detection of hepatocellular carcinoma in an early stage, before any clinical or even other laboratory abnormalities are evident. This detection of the small tumors in the early stages in Japan, but particularly in China and predominantly in Shanghai, has been rewarded with excellent chances of survival and possibly cure by surgical removal of the carcinoma, at this stage often still single.

These observations and successes have completely altered the clinical outlook in hepatocellular carcinoma and have led to the concept of subclinical hepatocellular carcinoma by the authors of this monograph. This concept represents major progress in the understanding, and particularly the management, of hepatocellular carcinoma, permitting "secondary prevention" at a time when primary prevention by immunization techniques such as vaccine and hyperimmune globulin is still a goal of the future. However, it has not yet been established whether the experiences in the Far East hold true for other parts of the world; in Africa there seems to be a tendency for more rapid growth of the hepatocellular carcinoma with less development of cirrhosis. Sufficient observational data are

not yet available for us to know whether or not this geographical difference is real, or to determine the predominant pattern in Western countries, aside from that in Oriental immigrants.

Nevertheless, this monograph, based on the study of an unusually large amount of material and its thorough laboratory evaluation, and supplemented by Chinese experiences with the basic aspects of the disease, should be of major interest to clinicians as well as to basic science-oriented physicians and other scientists all over the world, including the Western countries. It should assist them in understanding the problem and encourage them to repeat these studies in their own countries. The scientific community is indebted to Dr. Tang for making this information widely available.

New York, November 1984 Hans Popper, MD, PhD

Contributors

Cao Yun-zhen (Cao Y. Z.), Lecturer in Internal Medicine, Liver Cancer Research Unit, Zhong Shan Hospital, Shanghai First Medical College, Shanghai, P. R. China

Chen Hui-li (Chen H. L.), Associate Professor, Department of Biochemistry, Shanghai First Medical College, Shanghai, P. R. China

Chen Rui-ming (Chen R. M.), Senior Research Scientist (Professor), Ph. D., Head of Cancer Research Laboratory and Member of Scientific Council, Shanghai Institute of Cell Biology, Academia Sinica, Shanghai, P. R. China

Gu Tian-Jue (Gu T. J.), Professor and Head, Department of Biochemistry, Shanghai First Medical College, Shanghai, P. R. China

He Kai-ling (He K. L.), Associate Professor, Department of Biochemistry, Shanghai First Medical College, Shanghai, P. R. China

Li Mao-shen (Li M. S.), Associate Professor, Department of Biochemistry, Shanghai First Medical College, Shanghai, P. R. China

Lin Zhi-ying (Lin Z. Y.), Lecturer of Internal Medicine, Vice-Chairman of Liver Cancer Research Unit, Zhong Shan Hospital, Shanghai First Medical College, Shanghai, P. R. China

Shen Ding-wu (Shen D. W.), Research Associate (Assistant Professor), Cancer Research Laboratory, Shanghai Institute of Cell Biology, Academia Sinica, Shanghai, P. R. China

Tang Zhao-you (Tang Z. Y.), Professor of Surgery, Chairman of Liver Cancer Research Unit, Zhong Shan Hospital, Shanghai First Medical College, Shanghai, P. R. China

Wang Hen-wen (Wang H. W.), Senior Research Scientist (Professor), Group Leader of Environmental Carcinogenesis, Laboratory of Cancer Biology, Shanghai Institute of Cell Biology, Academia Sinica, Shanghai, P. R. China

Wen Yu-mei (Wen Y. M.), Associate Professor and Chairman of Department of Microbiology, Shanghai First Medical College, Shanghai, P. R. China

Xu He (Xu H.), Research Associate (Assistant Professor), Member of Environmental Carcinogenesis Group, Shanghai Institute of Cell Biology, Academia Sinica, Shanghai, P. R. China

Xu Zhi-zhang (Xu Z. Z.), Associate Professor and Chairman, Laboratory of Ultrasonic Diagnosis, Zhong Shan Hospital, Shanghai First Medical College, Shanghai, P. R. China

Yang Bing-hui (Yang B. H.), Lecturer in Internal Medicine, Liver Cancer Research Unit, Zhong Shan Hospital, Shanghai First Medical College, Shanghai, P. R. China

Yao Zhen (Yao Z.), Senior Research Scientist (Professor), Deputy Director of the Institute, Head of Department of Cancer Cell Biology, Shanghai Institute of Cell Biology, Academia Sinica, Shanghai, P. R. China

Ye Sheng-long (Ye S. L.), Doctor (Masters Degree), Liver Cancer Research Unit, Zhong Shan Hospital, Shanghai First Medical College, Shanghai, P. R. China

Ying Yue-ying (Ying Y. Y.), Professor and Vice-Chairman of Department of Pathology, Shanghai First Medical College, Shanghai, P. R. China

Yu Shun-zhang (Yu S. Z.), Associate Professor, Department of Epidemiology, Shanghai First Medical College, Shanghai, P. R. China

Yu Ye-qin (Yu Y. Q.), Associate Professor of Surgery, Vice-Chairman of Liver Cancer Research Unit, Zhong Shan Hospital, Shanghai First Medical College, Shanghai, P. R. China

Zhai Wei-rong (Zhai W. R.), Lecturer in Pathology, Department of Pathology, Shanghai First Medical College, Shanghai, P. R. China

Zhang Yu-yan (Zhang Y. Y.), Associate Scientist (Associate Professor), Shanghai Institute of Cell Biology, Academia Sinica, Shanghai, P. R. China

Zhen Qing-yi (Zhen Q. Y.), Research Associate (Assistant Professor), Head of the Division of Cancer Biochemistry, Shanghai Institute of Biochemistry, Academia Sinica, Shanghai, P. R. China

Zhou Xin-da (Zhou X. D.), Lecturer in Surgery, Liver Cancer Research Unit, Zhong Shan Hospital, Shanghai First Medical College, Shanghai, P. R. China

Zhou Yi-zhong (Zhou Y. Z.), Research Associate (Assistant Professor), Division of Cancer Biochemistry, Shanghai Institute of Biochemistry, Academia Sinica, Shanghai, P. R. China

Abbreviations

AFP	Alpha fetoprotein
AGD	Agar gel diffusion
ALD	Active-stage liver disease
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
anti-HBc	Antibody to hepatitis B core antigen
anti-HBe	Antibody to hepatitis B "e" antigen
anti-HBs	Antibody to hepatitis B surface antigen
CHCC	Clinical hepatocellular carcinoma
CIEP	Countercurrent immunoelectrophoresis
CT	Computed tomography
γ-GTP	Gamma glutamyl transpeptidase
HA	Hepatic angiography
HBcAg	Hepatitis B core antigen
HBeAg	Hepatitis B "e" antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
LDH	Lactate dehydrogenase
OT	Skin delayed hypersensitivity reaction to old tuberculin
PLC	Primary liver cancer
RIA	Radioimmunoassay
RN	Radionuclide imaging
RPHA	Reverse passive hemagglutination
RREA	Radiorocket electrophoresis autography
SCHCC	Subclinical hepatocellular carcinoma
US	Ultrasound, ultrasonography

Acknowledgements

The editor wishes to express his appreciation to Dr. Zhou X. D. and Dr. Ye S. L. for their help with the manuscripts.

The editor is also sincerely grateful to the following people for their contribution in clinical and research work at the Liver Cancer Research Unit, Zhong Shan Hospital, Shanghai First Medical College, Shanghai; Dr. Zhou N. Q., Dr. Lu J. Z., Dr. Tang C. L., Dr. Ma Z. C., and others.

The English of this manuscript has been improved by Professor Yang Chang-yi and Associate Professor Yao Zi-ran of the Department of Foreign Languages, Shanghai First Medical College, Shanghai, P.R. China.

Contents