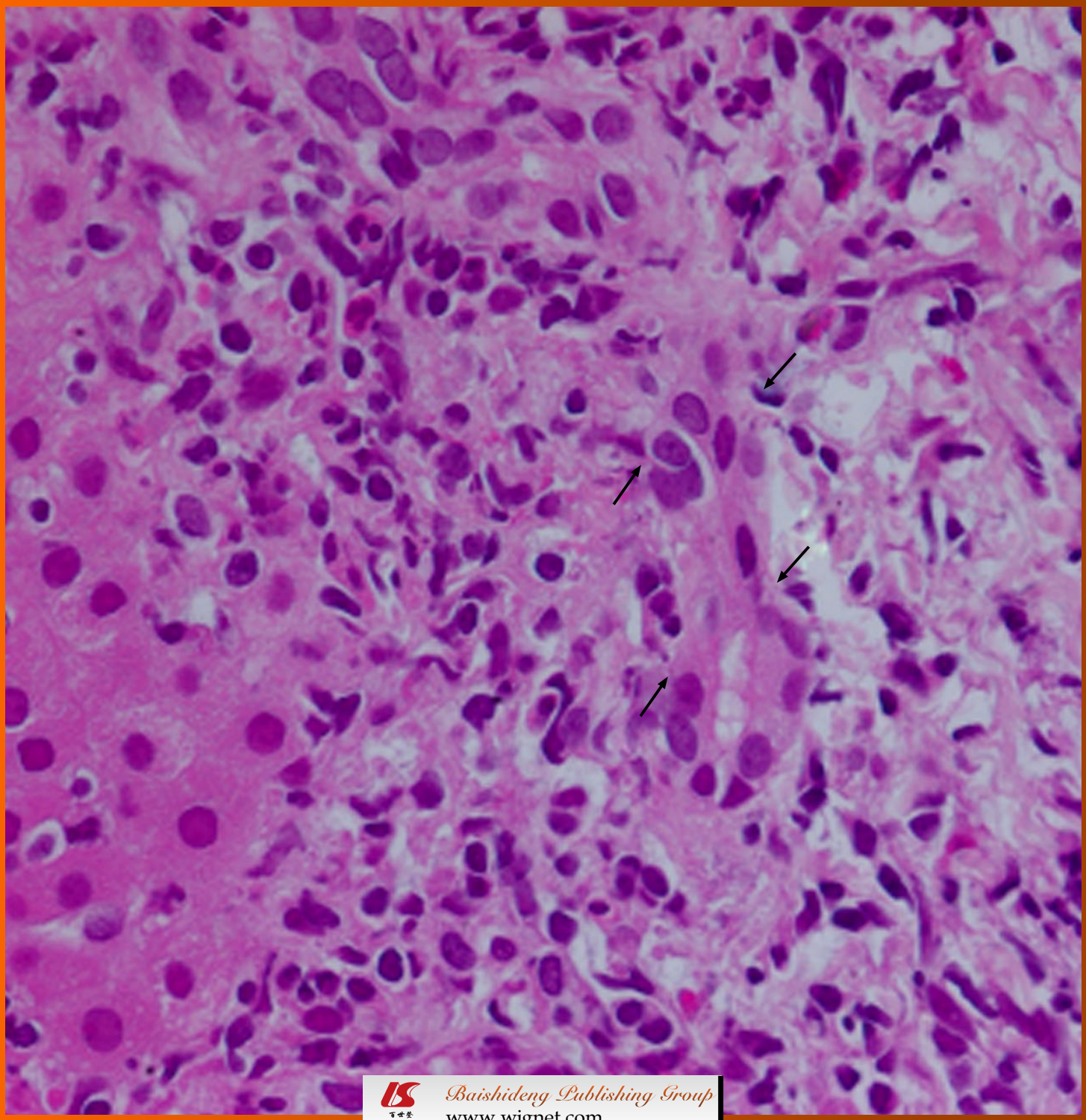
ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2010 October 27; 2(10): 367-394



Baishideng Publishing Group
www.wjgnet.com

WJH World Journal of Hepatology

A peer-reviewed, online, open-access journal of hepatology

Editorial Board

2009-2013

The *World Journal of Hepatology* Editorial Board consists of 572 members, representing a team of worldwide experts in hepatology. They are from 45 countries, including Argentina (4), Australia (7), Austria (2), Bangladesh (1), Belgium (3), Botswana (2), Brazil (8), Brunei Darussalam (1), Bulgaria (1), Canada (10), Chile (1), China (89), Egypt (3), Finland (1), France (15), Gambia (1), Germany (28), Greece (8), Hungary (3), India (20), Ireland (1), Israel (7), Italy (65), Japan (45), Malaysia (1), Mexico (4), Netherlands (4), Pakistan (2), Poland (1), Portugal (1), Philippines (1), Romania (1), Saudi Arabia (1), Singapore (4), South Korea (17), Spain (22), Sri Lanka (1), Sudan (1), Switzerland (2), Thailand (6), Tunisia (2), Turkey (13), United Kingdom (17), United States (144), and Venezuela (1).

Chiranjib Chakraborty, *Beijing*
Stephen Lam Chan, *Hong Kong*
George G Chen, *Hong Kong*
Min-Shan Chen, *Guangzhou*
Yang Cheng, *Shanghai*
Siu Tim Cheung, *Hong Kong*
Thomas YC Cheung, *Hong Kong*
Yick-Pang Ching, *Hong Kang*
William Chi-shing Cho, *Hong Kong*
Chui Chung-hin, *Hong Kong*
Shuang-Suo Dang, *Xi'an*
Yi-Tao Ding, *Nanjing*
Jian-Gao Fan, *Shanghai*
Yuen Man Fung, *Hong Kang*
Zuo-Jiong Gong, *Wuhan*
Tian-Quan Han, *Shanghai*
Jin-Yang He, *Guangzhou*
Garrett CL Ho, *Hong Kong*
Ji-Ming Hu, *Wuhan*
Can-Hua Huang, *Chengdu*
Zhi-Yong Huang, *Wuhan*
Jian-Hui Jiang, *Changsha*
Dong-Yan Jin, *Hong Kong*
Hsiang-Fu Kung, *Hong Kong*
Lai PBS Lai, *Hong Kong*
Wan YJ Lau, *Hong Kong*
Nancy WY Leung, *Hong Kong*
Jin-Qing Li, *Guangzhou*
Li-Ying Li, *Beijing*
Shu-Chen Li, *Harbin*
Xin-Wei Li, *Shanghai*
Yu-Yuan Li, *Guangzhou*
En-Qi Liu, *Xi'an*
Yin-Kun Liu, *Shanghai*
Chung-Mau Lo, *Hong Kong*
Lun-Gen Lu, *Shanghai*
Ming-De Lu, *Guangzhou*
John M Luk, *Hong Kong*
Guang-Hua Luo, *Changzhou*
Shuang Mei, *Shanghai*
Kelvin KC Ng, *Hong Kong*
Qin Ning, *Wuhan*
Qin Pan, *Shanghai*
Qi-Jun Qian, *Shanghai*
Jian-Min Qin, *Shanghai*
Xian-Jun Qu, *Jinan*
Xue-Ying Sun, *Harbin*
Qin Su, *Beijing*
Wu-Yi Sun, *Hefei*
Hui-Ru Tang, *Wuhan*
Peng Tao, *Nanning*
Eric WC Tse, *Hong Kong*
Bin Wang, Weifang
Xiao-Zhong Wang, *Fuzhou*
Xiu-Jie Wang, *Chengdu*
Zhen-Xia Wang, *Huhhot*
Grace LH Wong, *Hong Kong*
Nathalie Wong, *Hong Kong*
Xiong-Zhi Wu, *Tianjin*
De-Xiang Xu, *Hefei*
Rui-An Xu, *Quanzhou*
Xun-Di Xu, *Changsha*
Xiao Yang, *Beijing*
Zhen-Fan Yang, *Hong Kong*
Boon Hun Yong, *Hong Kong*
Ting-He Yu, *Chengdu*
Benny CY Zee, *Hong Kong*
Jia-Ning Zhang, *Dalian*
Xiao-Dong Zhang, *Tianjin*
Xiao-Lan Zhang, *Shijiazhuang*
Xiao-Yan Zhang, *Shanghai*
Hong-Chuan Zhao, *Hefei*
Xiao-Ping Zhao, *Beijing*
Jiang-Fan Zhu, *Shanghai*
Yi-Ping Zou, *Beijing*

Egypt

Nabil Mohie Abdel-Hamid, *Minia*
Laila AF Eissa, *Mansoura*
Mona Mostafa Fahmy Nosseir, *Giza*

Finland

Thomas Kietzmann, *Oulu*

France

Aramando Abergel, *Clenmont -Ferrant*
Henri Bismuth, *Villejuif Cedex*
Ana CFN Cardoso, *Paris*
Nicolas Chignard, *Paris*
Claude C de Fromentel, *Lyon*
Zdenko Herceg, *Lyon*
Nathalie Janel, *Paris*
Victor de Ledinghen, *Pessac cedex*
Antoinette Lemoine, *Villejuif*
Marcellin Patrick, *Clichy*
Raoul Poupon, *Paris*
Rodrigue Rossignol, *Bordeaux cedex*
Christian Trépo, *Lyon*
Dominique A Vuitton, *Besancon*
Virginie Wautot, *Pierre Benite*

Gambia

Maimuna Ebirunkeh Mendy, *Banjul*

Germany

Thomas Bock, *Tuebingen*
Ali Canbay, *Essen*
Enrico Narciso De Toni, *München*
Joachim Drevs, *Freiburg*
Volker Fendrich, *Marburg*
Peter R Galle, *Mainz*
Erich Gulbins, *Essen*
Roland Kaufmann, *Jena*
Sebastian Hinz, *Kiel*
Philipp Kobbe, *Aachen*
Michael Kremer, *Heidelberg*
Christian Liedtke, *Aachen*
Martin Loss, *Regensburg*
Arun Kumar Mankan, *Munich*
Lars Müller, *MD, Kiel*
Michael D Menger, *Saarbrucken*
Andreas K Nussler, *Munich*
Margarete Odenthal, *Koeln*
Claus Petersen, *Hannover*
Andrej Potthoff, *Hannover*
Thomas Pusl, *München*
Elke Roeb, *Giessen*
Frank Tacke, *Aachen*
Stefan Rose-John, *Kiel*
Andreas Teufel, *Mainz*
Lothar Thomas, *Frankfurt*
Jens JW Tischendorf, *Aachen*
Arndt Vogel, *Hannover*

Greece

Alex P Betrosian, *Athens*
Spiros G Delis, *Athens*
Ioannis Diamantis, *Athens*
Papandreou Dimitrios, *Mela*
Elias A Kouroumalis, *Crete*
George Papatheodoridis, *Athens*
Stamatios E. Theocharis, *Athens*

Hungary

Gábor Bánhegyi, *Budapest*
Subhamay Ghosh, *Pécs*
Peter Nagy, *Budapest*

India

Anjali Deepak Amarapurkar, *Mumbai*
DN Amararpurkar, *Mumbai*
Runu Chakravarty, *Kolkata*
Pronobesh Chattopadhyay, *Moradabad*
Puneet Chopra, *Gurgaon Haryana*
Tanya Das, *Kolkata*
Radha Krishan Dhiman, *Chandigarh*
Ajay Duseja, *Chandigarh*
Devendra K Gupta, *New Delhi*
P Kar, *New Delhi*
Sudhir Kumar, *Lucknow*
Vijay Kumar, *New Delhi*
Anoop Misra, *New Delhi*
Devendra Parmar, *Lucknow*
Rajendra Prasad, *Chandigarh*
K Rajeshwari, *New Delhi*
Pallu Reddanna, *Hyderabad*
Barjesh Chander Sharma, *New Delhi*
Sarman Singh, *New Delhi*
Ajith TA, *Thrissur*

Ireland

Matthew William Lawless, *Dublin*

Israel

Yaron Ilan, *Jerusalem*
Yaakov Maor Kendler, *Tel Hashomer*
Ran Oren, MD, *Tel Aviv*
Amir Shlomai, *Modiin*
Rifaat Safadi, *Jerusalem*
Shira Zelber Sagi, *Tel Aviv*
Yehuda Julius Shoenfeld, *Tel Hahsomer*

Italy

Luca Aasaloni, *Bologna*
Giovanni Addolorato, *Rome*
Luigi E Adinolfi, *Naples*
Pietro Andreone, *Bologna*
M Appetecchia, *Rome*
Antonio Ascione, *Napoli*
Ferruccio Bonino, *Milano*
Bruno D Bruno, *Benevento*
Savino Bruno, *Milano*
Melchiorre Cervello, *Palermo*
Claudio Chiesa, *Rome*
Stefano Colagrande, *Firenze*
Massimo G Colombo, *Milan*
Samuele De Minicis, *Montegranaro*
Alessandro Vitale, *alessandro*
Fabio Farinati, *Padova*
Paolo Feltracco, *Padova*
Domenico Ferri, *Bari*
Amalia Gastaldelli, *Pisa*
Domenico Girelli, *Verona*
Fernando Goglia, *Benevento*
Alessandro Grasso, *Savona*
Ignazio Grattagliano, *Bari*
Pietro Invernizzi, *Milan*
Francesco Izzo, *Naples*
Amedeo Lonardo, *Modena*
Malaguarnera Lucia, *Trecastagni*
Massimo Di Maio, *Rossano*
Melania Manco, *Rome*
Andrea Mancuso, *Palermo*
F Marotta, *Milano*
Fabio Marra, *Florence*
Roberto Mazzanti, *Florence*
Giulia Morsica, *Milan*
Antonio Moschetta, *Bari*
Massimo Negrini, *Ferrara*
Andrea Nicolini, *Pisa*
Giuseppe R Nigri, *Rome*
Valerio Nobili, *Rome*
Valentina Pallottini, *Rome*
Adriano M Pellicelli, *Rome*
Marcello Persico, *Naples*
Massimo Pinzani, *Firenze*
Giovanni Polimeni, *Messina*
Camillo Porta, *Pavia*
Piero Portincasa, *Bari*
Emilio Quaia, *Trieste*
Giuseppe Remuzzi, *Bergamo*
Domenico Ribatti, *Bari*
Massimo Roncalli, *Rozzano*
Carlo Sabbà, *Bari*
Orazio Schillaci, *Rome*
Gaetano Serviddio, *Foggia*
Aurelio Sonzogni, *Bergamo*
Paolo Sorrentino, *Salerno*
Enea Spada, *Roma*
Giovanni Tarantino, *Naples*
Luciano Tarantino, *Naples*
Claudio Tiribelli, *Trieste*
Pierluigi Toniutto, *Udine*
Pietro Vajro, *Naples*
Luca Vigano, *Torino*

Japan

Yuichiro Eguchi, *Saga*
Munechika Enjoji, *Fukuoka*
Jiro Fujimoto, *Osaka*
Atsushi Hosui, *Osaka*
Kazuo Ikeda, *Nagoya*
Toru Ishikawa, *Niigata*
Yoshiaki Iwasaki, *Okayama*
Satoru Kakizaki, *Gunma*
Naoya Kato, *Tokyo*
Takumi Kawaguchi, *Kurume*
Kiminori Kimura, *Tokyo*
Tsuneo Kitamura, *Chiba*
Keiichi Kubota, *Tochigi*
Sabina Mahmood, *Okayama*
Hitoshi Maruyama, *Chiba*
Sachiko Matsuhashi, *Saga*
Toshihiro Mitaka, *Sapporo*
Eiji Miyoshi, *Yamada-oka Suita*
Zenichi Morise, *Toyoake Aichi*
Ryuichi Morisihita, *Osaka*
Yoshiki Murakami, *Kyoto*
Satoru Murata, *Tokyo*
Atsushi Nakajima, *Kanagawa*
Yasuni Nakanuma, *Kanazawa*
Waka Ohishi, *Hiroshima*
Morikazu Onji, *Matsuyama*
Toshiji Saibara, *Nankoku*
Hiroaki Shiba, *Tokyo*
Ikuo Shoji, *Hyogo*
Ryo Sudo, *Yokohama*
Yoshio Sumida, *Nara*
Shinji Tanaka, *Tokyo*
Takuji Tanaka, *Gifu*
Akihiko Tsuchida, *Tokyo*
Takato Ueno, *Kurume*
Shinichi Ueno, *Kagoshima*
Kiyohito Yagi, *Osaka*
Yo-ichi Yamashita, *Hiroshima*
Teruyoshi Yanagita, *Saga*
Shuang-Qin Yi, *Kanazawa*
Hiroshi Yoshida, *Tokyo*
Hitoshi Yoshiji, *Nara*

Malaysia

Kamsiah Jaarin, *Kuala Lumpur*

Mexico

Norberto C Chavez-Tapia, *Tlalpan*
Javier Lizardi Cervera, *Tlalpan CP*
Saúl Villa-Treviño, *México DF*
Florencia V Vorackova, *México DF*

Netherlands

Robert Jacobus de Knegt, *Rotterdam*
TU Hoogenraad, *Heidelberglaan*
Maarten E Tushuizen, *MB Amsterdam*
Robert C Verdonk, *RB Groningen*

Pakistan

Syed Hamid Ali, *Karachi*
Huma IQ TI, *Islamabad*

Poland

Maria ES Lotowska, *Bialystok*

Portugal

Felix Dias Carvalho, *Porto*

Philippines

Janus P Ong, *Manila*

Romania

Eugen Georgescu, *Craiova*

Saudi Arabia

Ahmed Helmy, *Riyadh*

Singapore

Wei Ning Chen, *Singapore*
Si-Shen Feng, *Singapore*
Lang Zhuo, *Singapore*
Chun-Tao Wai, *Singapore*

South Korea

Sang Hoon Ahn, *Seoul*
Sun Pyo Hong, *Yongin*
Byung Ihn Choi, *Seoul*
Seok Joo Han, *Seoul*
Kyung Lib Jang, *Busan*
Bum-Joon Kim, *Seoul*
Dong Goo Kim, *Seoul*
Kyung Sik Kim, *Seoul*
Meehyein Kim, *Yongin*
Young Chul Kim, *Seoul*
Mi-Kyung Lee, *Jeonnam*
Young-Ik Lee, *Taejon*
Kwan-Kyu Park, *Daegu*
Hyunchul Rhim, *Seoul*
In Kyoung Lim, *Gyunggi-do*
Dae-Yeul Yu, *Daejeon*
Jong Won Yun, *Kyungbuk*

Spain

Jose AG Agundez, *Badajoz*
Maria Angeles, *Madrid*
Agustin Castiella, *Mendaro*
Ruben Ciria, *Cordoba*
Joan Clari, *Barcelona*
Maria Buti Ferret, *Barcelona*

Puri Fortes, *Pamplona*
Joan Genescà, *Barcelona*
María J Gómez-Lechón, *Valencia*
Arias Jaime, *Madrid*
Ángeles Pajares María, *Madrid*
Jordi Muntane, *Cordoba*
Jose JG Marin, *Salamanca*
Julia P Onsurbe, *Barcelona*
Albert Parés, *Barcelona*
Sonia Ramos, *Madrid*
Cristina Ripoll, *Madrid*
Isabel F Romero, *Barcelona*
Marta R Romero, *Salamanca*
Juan Macias Sanchez, *Sevilla*
Juan Sastre, *Valencia*
Manuel Vázquez-Carrera, *Barcelona*

Sri Lanka

EGD Shaman Rajindrajith, *Ragama*

Sudan

Hatim MY Mudawi, *Khartoum*

Switzerland

Beat Mullhaupt, *Zurich*
Maurer A Christoph, *Liestal*

Thailand

Nattiya Hirankarn, *Bangkok*
Somchai Pinlaor, *Khon Kaen*
Yong Poovorawan, *Bangkok*
Abhasnee Sobhonslidsuk, *Bangkok*
Chanitra Thuwajit, *Bangkok*
Sopit Wongkham, *Khon Kaen*

Tunisia

Olfa Bahri, *Tunis-Belvedere*
Chadli Dziri, *Tunis*

Turkey

Inci Alican, *Istanbul*
Ahmet Atessahin, *Elazig*
Yasemin Hatice Balaban, *Ankara*
Hayrullah Derici, MD, *Izmir*
Cigdem Ulukaya Durakbasa, *Istanbul*
Muhsin MM Harputluoglu, *Malatya*
Abdurrahman Kadayifci, *Gaziantep*
Adnan Kadayifci, *Antalya*
Ali Sazci, *Kocaeli*
Ilker Tasci, *Ankara*
Mehmet Yalniz, *Elazig*
Serkan Yener, *Izmir*
Yusuf Yilmaz, *Istanbul*

United Kingdom

Alastair David Burt, *Newcastle*
David O Cosgrove, *London*
Anil Dhawan, *London*
Indra Neil Guha, *Nottingham*
Phillip M Harrison, *London*
Hübscher SG Hübscher, *Birmingham*
Long R Jiao, *London*
AT Koulaouzidis, *Edinburgh*
Patricia Lalor, *Birmingham*
David A Lomas, *Cambridge*
Rajeshwar P Mookerjee, *London*
Gareth J Morris-Stiff, *Wales*
Kathryn L Nash, *Southampton*
Derek Anthony O'Reilly,
Christian P Selinge, *Bolton*
Konstantinos Tziomalos, *London*
Feng Wu, *Oxford*

United States

Gary A Abrams, *Montgomery*
Hassan H A-Kader, *Tucson*
Hans-Olov Adami, *Massachusetts*
Joseph Ahn, *Maywood*
Shannon Marie Bailey, *Alabama*
Numan Cem Balci, *St Louis MO*
Edmund J Bini, *New York*
Victor E Buckwold, *Frederick*
Roniel Cabrera, *Gainesville*
Guoqing Cao, *Indiana*
Disaya Chavalitdhamrong, *New York*
Chien-Shing Chen, *Loma Linda*
Fei Chen, *Morgantown*
Su Chen, *San Antonio*
Youhai H Chen, *Philadelphia*
Anne M Covey, *New York*
Mark J Czaja, *New York*
Srikanta Dash, *New Orleans*
Anthony JB Demetris, *Pittsburgh*
Sridevi Devaraj, *California*
Lisa Ross Dixon, *Gainesville*
Terrence M Donohue, *Omaha*
Q Ping Dou, *Detroit*
Murray N Ehrinpreis, *Detroit*
Marwan Ghazi Fakih, *Buffalo*
Shengyun Fang, *Maryland*
Claus J Fimmel, *Illinois*
Robert Anthony Fisher, *Virginia*
Samuel W French, *Torrance*
Phillip A Furman, *Princeton*
M Eric Gershwin, *California*
Jalal K Ghali, *Michigan*
Grace Liejun Guo, *Kansas City*
Dieter Haemmerich, *Charleston*
Young S Hahn, *Charlottesville*
Stephen A Harrison, *Texas*
Dee Harrison-Findik, *Nebraska*
Sidhartha Hazari, *Louisiana*
Thomas S Helling, *Jackson*
Alan W Hemming, *Florida*
Iryna S Hepburn, *Evans*
Ai-Xuan L Holterman, *Chicago*
Ke-Qin Hu, *California*
Guangcun Huang, *Ohio*
Wendong Huang, *California*
Rachel M Hudacko, *New Brunswick*
Michael John Jacobs, *Michigan*
Hartmut W Jaeschke, *Kansas City*
Ravi Jhaveri, *North Carolina*
Lynt B Johnson, *Washington*
Neil Louis Julie, *Bethesda*
Sanjay Kakar, *San Francisco*
Sanjeeva P Kalva, *Boston*
Jing X Kang, *Massachusetts*
Hetal Karsan, *Georgia*
Emmet B Keeffe, *California*
Nancy Ellen Kemeny, *New York*
Andrew Scott Kennedy, *Cary*
Kusum K Kharbanda, *Omaha*
David H Kirn, *California*
Hyam Lerner Leffert, *La Jolla*
Stacee Marie Lerret, *Milwaukee*
Fengzhi Li, *New York*
Wei Li, *Houston*
Shuang Liu, *Indiana*
Su Hao Lo, *Davis*
Daniel G Maluf, *Richmond*
Jose E Manautou, *Storrs*
Richard S Mangus, *Indiana*
Mary Ko Manibusan, *Virginia*
Paul Martin, *Miami,*
Jochen Mattner, *Ohio*
James A McCubrey, *North Carolina*
Valentina Medici, *Sacramento*
George Michalopoulos, *Pittsburgh*
Smruti R Mohanty, *Illinois*
John T Moore, *GlaxoSmithKline*
Ravi Murthy, *Texas*
Laura E Nagy, *Cleveland*
Sagar U Nigwekar, *Rochester*
Eileen M O'Reilly, *New York*
Kevin FS O'Carroll, *Hershey*
Melissa Kay Osborn, *Atlanta*
Helieh Saatara Oz, *Kentucky*
Igor P Pogribny, *Arkansas*
Nicholas C Popescu, *Bethesda Maryland*
Daniel S Pratt, *Boston*
Ratna B Ray, *Louis*
Nancy Reau, *Chicago*
Janardan K Reddy, *Chicago*
Martin J Ronis, *Little Rock*
Phillip Ruiz, *Florida*
Tanios B Saab, *Columbus*
Adnan Said, *Madison*
Neeraj Saxena, *Georgia*
Raymund R Saxena, *Minnesota*
Ann Scheimann, *Baltimore*
Timothy M Schmitt, *Charlottesville*
Bernd Schnabl, *La Jolla*
Kunwar Shailubhai, *Pennsylvania*
Muhammad Y Sheikh, *California*
Perry Shen, *Winston-Salem*
Viji Shridhar, *Rochester*
Shivendra D Shukla, *Missouri*
Ashwani K Singal, *Galveston*
Keshav K Singh, *New York*
Omar Skalli, *Shreveport*
Byoung-Joon Song, *Maryland*
Branko Stefanovic, *Tallahassee*
Stephen Strom, *Pennsylvania*
Xiao Su, *San Francisco*
Wing-Kin Syn, *North Carolina*
Gyongyi Szabo, *Massachusetts*
Shinako Takada, *Houston*
Yueming Tang, *Chicago*
John M Taylor, *Philadelphia*
Swee H The, *Springfield*

WJH World Journal of Hepatology

Contents

Monthly Volume 2 Number 10 October 27, 2010

World Journal of Hepatology
Volume 2 Number 10 October 27, 2010

Contents

NAME OF JOURNAL
World Journal of Hepatology

LAUNCH DATE
October 31, 2009

SPONSOR
Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

EDITING
Editorial Board of *World Journal of Hepatology*,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-5908-0038
Fax: +86-10-8538-1893
E-mail: wjh@wjgnet.com
http://www.wjgnet.com

PUBLISHING
Baishideng Publishing Group Co., Limited,
Room 1701, 17/F, Henan Bulding,
No.90 Jaffe Road, Wanchai,
Hong Kong, China
Fax: 00852-3115-8812
Telephone: 00852-5804-2046
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

SUBSCRIPTION
Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

ONLINE SUBSCRIPTION
One-Year Price 216.00 USD

PUBLICATION DATE
October 27, 2010

CSSN
ISSN 1948-5182 (online)

EDITORIAL OFFICE
Hai-Ning Zhang, Director
World Journal of Hepatology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-5908-0038
Fax: +86-10-8538-1893
E-mail: wjh@wjgnet.com
http://www.wjgnet.com

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1948-5182/g_info_20100316080002.htm. If you do not have web access please wcontact the editorial office.

ONLINE SUBMISSION
http://www.wjgnet.com/1948-5182office

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v2.i10.367

World J Hepatol 2010 October 27; 2(10): 367-373
ISSN 1948-5182 (online)

EDITORIAL

Liver-specific therapies for metastases of neuroendocrine pancreatic tumors

Volker Fendrich, Patrick Michl, Nils Habbe, Detlef Klaus Bartsch

Volker Fendrich, Nils Habbe, Detlef Klaus Bartsch, Department of Surgery, Philipps-University, Marburg D-35043, Germany
Patrick Michl, Department of Gastroenterology, Philipps-University, Marburg D-35043, Germany
Author contributions: Fendrich V, Michl P and Habbe N reviewed the literature and contributed to different sections of the manuscript; and Bartsch DK revised the manuscript.
Correspondence to: Volker Fendrich, MD, Department of Surgery, Philipps University Marburg, Baldingerstraße, Marburg D-35043, Germany. fendrich@med.uni-marburg.de
Telephone: +49-642-12862582 Fax: +49-642-12863851
Received: July 1, 2010 Revised: October 5, 2010
Accepted: October 12, 2010
Published online: October 27, 2010

Abstract

The presence or development of liver metastases in patients with neuroendocrine pancreatic tumors is the most important prognostic factor. Liver resection, transplantation and many different therapeutic approaches are discussed in this special review.

Key words: Liver metastasis; Neuroendocrine pancreatic tumor; Liver resection; Liver transplantation; Chemotherapy; Biotherapy

Peer reviewers: Derek Anthony O'Reilly, PhD, FRCS, Department of Surgery, North Manchester General Hospital, Delaunays Road, Manchester, M8 5RB, United Kingdom; Andrea Nicolini, Professor, Department of Internal Medicine, University of Pisa, via Roma 67, Pisa 56126, Italy; Eileen M O'Reilly, Associate Member, MSKCC, Associate Professor, Cornell University Medical Center, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 324, New York, NY 10065, United States

Fendrich V, Michl P, Habbe N, Bartsch DK. Liver-specific therapies for metastases of neuroendocrine pancreatic tumors. *World J Hepatol* 2010; 2(10): 367-373 Available from: URL: http://www.wjgnet.com/1948-5182/full/v2/i10/367.htm DOI: http://dx.doi.org/10.4254/wjh.v2.i10.367

INTRODUCTION

Pancreatic endocrine tumors (PETs) represent an important subset of pancreatic neoplasms (Table 1). These tumors account for 2%-4% of all clinically detected pancreatic tumors. They consist of single or multiple benign or malignant neoplasms, and are associated with multiple endocrine neoplasia type 1 (MEN1) in 10%-20%[1]. PETs are rare but fascinating tumors. PETs present as either functional tumors, causing specific hormonal syndromes, like Zollinger-Ellison-Syndrome (ZES) or organic hyperinsulinism, or as non-functional PETs (NFPETs) with symptoms similar to pancreatic adenocarcinomas[1,2]. The total incidence of all PETs is approximately 1 in 100 000 people/year[1,2].

NATURAL HISTORY AND PROGNOSIS

The natural history of PETs is highly variable (Table 1)[3]. Small, benign neoplasms, such as 90% of all sporadic insulinomas, are readily curable by surgical resection. The incidence of insulinomas that are malignant is about 10%. Insulinomas greater than 2 cm in diameter without signs of angioinvasion or metastases are considered benign. Surgery cures all patients with benign insulinomas. Danforth and co-authors reviewed 62 cases of metastatic insulinoma[4]. All tumors had metastases, most commonly to the liver and/or lymph nodes. The recurrence rate was 63%, with the median interval to recurrence of 2.8 years. The median survival for patients with recurrent tumors was 19 mo. Palliative resection was associated with a median survival of 4 years, and in those who had a biopsy only it was 11 mo[4]. Although most gastrinomas grow slowly, 60%-90% are malignant (Figure 1). Patients with metastatic gastrinoma have 5-year survival rates of only 20%-38%. Several studies have provided information on the biological behavior of pancreatic and duodenal gastrinomas. It has been shown that both locations are equally malignant, with 40%-70% of patients presenting with metastases. The postoperative disease-free survival rates for both

Table 1 Neuroendocrine tumors of the pancreas

Tumor type (syndrome)	Incidence of PETs (%)	Clinical presentation	Malignancy (%)
Insulinoma	70-80	Weakness, sweating, tachycardia, anxiety, fatigue, headache, dizziness, disorientation, seizures and unconsciousness	< 10
Gastrinoma	20-25	Intractable or recurrent peptic ulcer disease (hemorrhage, perforation), complications of peptic ulcer, diarrhea	50-60
Non-functional tumors	30-50	Obstructive jaundice, pancreatitis, epigastric pain, duodenal obstruction, weight loss, fatigue	60-90
VIPoma	4	Profuse watery diarrhea, hypotension, abdominal pain	80
Glucagonoma	4	Migratory, necrolytic skin rash, glossitis, stomatitis, angular cheilitis, diabetes, severe weight loss, diarrhea	80
Somatostatinoma	< 5	Weight loss, cholelithiasis, diarrhea, neurofibromatosis	50
Carcinoid	< 1	Flushing, sweating, diarrhea, edema, wheezing	90
ACTHoma	< 1	Cushing's syndrome	> 90
GRFoma	< 1	Acromegaly	30
PTH-like-oma	< 1	Hypercalcemia, bone pain	> 90
Neurotensinoma	< 1	Hypotension, tachycardia, malabsorption	> 80

PETs: pancreatic endocrine tumors.

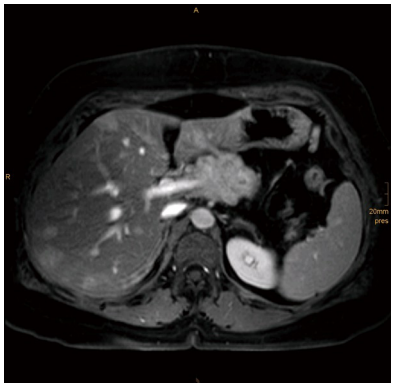


Figure 1 Pancreatic gastrinoma with multiple liver metastases.

tumor types are similar, that is, between 30%-50% after 10 years for sporadic gastrinoma and < 10% for MEN1-related gastrinoma[1,5,6]. Duodenal tumors, however, are smaller, less likely to metastasize to the liver, and have a better prognosis than pancreatic gastrinomas[5]. Most other functional, and all malignant NFPETs, also have a less favourable prognosis. Approximately 50%-80% of these neoplasms recur or metastasize, and up to one-third of patients already have metastases at initial presentation[3]. Historic controls with untreated liver metastases have a 5-year survival rate of only 20%-30%[7]. The natural history of pancreatic tumors in MEN1 patients is difficult to define. Approximately 50% of MEN1-associated pancreatic neoplasms are NFPETs[8]. NFPETs rarely become symptomatic in patients and are commonly detected during regular screening, using CT or MRI. PETs in MEN1 patients usually occur in multiples and NFPETs often coexist beside a clinically dominant functioning lesion. The prevalence of PETs in MEN1 patients is 80%-100%. It is the most common disease-related cause of death, and one should assume that all PETs have the biological ability to develop distant metastases[9]. Patients with PETs generally have a much better prognosis than those with pancreatic adenocarcinoma. Recent studies have reported improved survival after resection; in one study, the median overall survival in resected patients was 58-97 mo, compared with 15-21 mo in patients not undergoing surgery, although the number of patients with information regarding the surgery was small[10]. It is noteworthy that in almost every study, the presence or development of liver metastases, but not lymph-node metastases, is the most important prognostic factor[1,3].

Repeated resections for resectable recurrences or metastases are thought to be indicated in order to improve survival[11]. If an aggressive approach is used, potentially curative resections are possible in up to 62% of patients, and overall, 5-year survival rates of 65% can be achieved[8,11,12]. Debulking resections may also be appropriate. In a study of 170 patients with liver metastases from neuroendocrine tumors, major hepatectomy was performed in 91 patients (54%). The postoperative complication rate was 14%, and two patients died (1.2%). Surgery controlled symptoms in 104 out of 108 patients, but the recurrence rate at 5 years was 59%. Overall survival was 61% and 35% at 5 and 10 years respectively. The authors concluded that debulking extends survival, although recurrence is expected[13]. Removal of the primary tumor in non-metastatic patients may significantly improve survival, compared with that of patients who have not undergone successful primary tumor resection[14]. Solorzano *et al*[15] reported survival data for 163 patients with NFPETs. As expected, patients with localized, non-metastatic disease at the time of diagnosis had a significantly superior median survival compared to those with metastatic disease (7.1 *vs* 2.2 years, $P < 0.0001$). Among those with localized disease, an additional survival advantage was demonstrated for patients who underwent complete resection of the primary tumor, compared to those with locally advanced unresectable tumors (7.1 *vs* 5.2 years)[15].

LIVER RESECTION

An increasing number of studies on surgical treatment of neuroendocrine tumors with liver metastases have been published[15-21] (Figure 2). Although none of these stud-

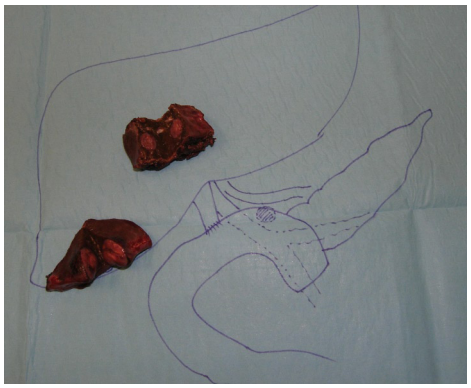


Figure 2 Operative specimen of liver metastases of a non-functional pancreatic endocrine tumor.

ies was a randomized clinical trial, and most of them had a varied proportion of patients with PETs and patients with midgut carcinoid tumors, nevertheless important conclusions can be drawn. In these studies, a total of 118 patients with hepatic metastases from PETs were treated, mostly by surgical resection. There was an average operative mortality of 3% and a 5-year survival rate of 64%[15-21]. In a study by Touzios *et al*[16] the median and 5-year survival were only 20 mo and 25% for patients with their liver metastases treated in a non-aggressive way compared with over 96 mo and 72% for those who had undergone hepatic resection and/or radiofrequency ablation of their liver metastases. In a study by Fendrich *et al*[11], 27 patients with metastases from PETs were treated surgically and 5 and 10-year survival rates of 81% and 72% was achieved. These data are very encouraging, compared with historic controls, where patients with metastatic PETs remained untreated and had a 5-year survival rate of only 30%-40%[22,23]. Que *et al* reviewed the data for 212 patients with partial hepatectomy for metastatic neuroendocrine tumors. The overall morbidity rate was 14%, while the operative mortality rate after partial hepatectomy for metastatic carcinoid disease was 2.3%[24]. However, the favourable outcome observed could be biased, because most of the non-resectable patients with advanced disease were included in the non-surgical group. Therefore, while studies indicate that surgery could benefit some patients with limited liver disease, the best management approach remains inconclusive.

LIVER TRANSPLANTATION

Approximately 120-130 cases of orthotopic liver transplantation for PETs have been published, but long-term follow-up data have been limited, and the individual series were small[25]. Taken together, the data confirm that cure by transplantation is rare. The largest single-center analysis was recently published by Rosenau *et al*[26], reporting on 19 patients who received orthotopic liver transplantation for metastatic NET. The authors reported 1-, 5- and 10-year survival rates of 89, 80 and 50%, respectively. All deaths during long-term follow-up were tumor-associated. Recurrence was diagnosed in 12 patients between 2 wk and 48 mo after the procedure. Orthotopic liver transplantation should therefore only be considered in selected young patients with metastases limited to the liver, and those with a previously resected primary PET who require relief from hormonal or tumor symptoms.

MEDICAL THERAPY

If surgical resection or interventional embolization of the hepatic tumor burden is not feasible, or if the metastases are not confined to the liver, systemic treatment remains the only option. Among systemic therapies, two main approaches have to be considered: biotherapy using somatostatin analoga, interferon or novel multi-targeting agents, and conventional cytoreductive chemotherapy. The choice of therapeutic option depends on the biological behavior of the tumor according to clinical or histopathological parameters, such as grading and proliferation index (Ki67). Furthermore, the localization of the primary tumor (foregut, midgut and hindgut) has to be taken into account, with midgut tumors generally responding less well to systemic chemotherapy, compared to foregut tumors. By definition, none of the systemic therapies is liver-specific, but act on all metastatic sites. In the following section, the main biotherapies and chemotherapeutic regimens will be described.

BIOTHERAPY

Somatostatin analoga are the primary treatment for patients with hormonal symptoms of neuroendocrine tumors of the midgut presenting with carcinoid syndrome. The antisecretory effect of somatostatin analogues results in symptomatic improvement in 40%-80% of the patients[27,28]. In the PROMID study, Rinke *et al*[29] recently provided evidence that a long-acting somatostatin analoga, octreotide LAR, not only provides symptomatic relief, but also mediates anti-proliferative effects by significantly lengthening the time to tumor progression compared with placebo in patients with functionally active and inactive metastatic midgut NETs.

In addition, somatostatin analoga are able to improve symptoms caused by foregut NETs, such as VIPoma and glucagonoma, by overcoming diarrhea and skin rash[28]. In insulinomas, somatostatin analoga have to be used with great caution, since hypoglycemia can deteriorate due to the concomitant suppression of growth hormone and glucagon[28].

Usually, short-acting analoga, such as octreotide, are initially given to test the individual's tolerance, and side effects such as diarrhea and abdominal discomfort. If tolerated well, depot formulations such as octreotide-LAR i.m. or lanreotide autogel s.c. are applied every 4 wk, with the efficacy of lanreotide and octreotide being comparable[28,30,31]. Major side effects of somatostatin analoga may include gallstone formation and, sometimes, but rarely, persistent steatorrhea[28].

Besides somatostatin analoga, interferon-alpha represents the second choice among biotherapies. It acts both directly and indirectly on the tumor cells by inhibiting protein and hormone synthesis and by modulating immune response[28]. To date, recombinant IFN-alpha2a and IFN-alpha2b and their pegylated forms are being used in clinical situations. Interferon has been demonstrated as similarly effective in symptom control when compared to somatostatin analoga, with biochemical responses occurring in 40%-60%, and symptomatic improvement in 50%-60%[32]. However, partial tumor remission could only be noted in 10%-15% of the patients. Due to a larger range of side effects such as flu-like syndrome, weight loss, fatigue, autoimmune reactions and depression, interferon is generally used as a second-line therapy for symptomatic control[32].

CHEMOTHERAPY

Chemotherapy in gastrointestinal neuroendocrine tumors is mainly reserved for poorly differentiated metastatic tumors, but may also be used in selected well or moderately differentiated carcinomas which are either not eligible or resistant to other therapies. Generally, foregut tumors respond better to cytoreductive chemotherapies when compared to midgut tumors.

In most metastatic foregut tumors, first-line treatment consists of streptozotocin (STZ) in combination with 5-FU or doxorubicin, achieving a response rate of between 39%-63%[33,34]. In poorly differentiated, highly proliferating tumors (Ki67 > 20%), cisplatin or carboplatin in combination with etoposide are being used in analogy to regimens used for small-cell lung cancer[28]. With this regimen, response rates can be achieved in up to 67% of the patients[35]. At initiation of chemotherapy, all functionally active tumors should be treated concomitantly with somatostatin analoga in order to avoid a hormonal crisis due to cell lyses[28]. Several agents including temozolomide[36] and thalidomide[37] have been positively evaluated in clinical trials, representing alternative strategies after failure of standard chemotherapies.

For patients with metastatic midgut or hindgut tumors, the results with systemic chemotherapy have been generally poor, with response rates below 10%[28]. It is therefore generally not indicated except in poorly differentiated neuroendocrine carcinomas.

NEW TARGETED AGENTS

During recent years, several small molecule inhibitors targeting one or several kinases have been, or are currently being evaluated in clinical trials, including the multi-kinase inhibitor sunitinib[38] and the mTOR inhibitor everolimus[39]. A recent phase II trial tested everolimus +/- long-acting somatostatin analoga: Everolimus alone resulted in stable disease rates of 68.7% (PFS 9.7 mo), in combination with somatostatin analoga in 77.8% of the patients (PFS 16.7 mo) in patients with pancreatic NETs progressive after chemotherapy[39]. Furthermore, new somatostatin analoga such as pasireotide or anti-angiogenetic strategies using anti-VEGF agents are also being clinically evaluated.

SOMATOSTATIN RECEPTOR RADIONUCLIDE THERAPY

The fact that most neuroendocrine midgut tumors express somatostatin receptors can be used for therapeutic targeting of these receptors with radio-labeled somatostatin analoga. Different analoga have been investigated for somatostatin receptor radionuclide therapy (SRRT), (^{90}Y-DOTA-Tyr3) octreotide and (^{177}Lu-DOTA-Tyr3) octreotate[40], with response rates of up to 35%, according to phase Ⅰ and Ⅱ trials in patients with progressive disease[28,40]. Generally, SRRT is indicated in metastatic endocrine midgut tumors with a positive somatostatin receptor scintigraphy which failed other therapies, in particular, in cases where the metastatic load is not only confined to the liver.

INTERVENTIONAL APPROACHES IN THE TREATMENT OF LIVER METASTASES

Interventional strategies and procedures provide a multitude of options in the treatment of neuroendocrine liver metastases. The main aim of these procedures is firstly, the control of hormonal symptoms in patients with active tumors, and secondly, to control tumor growth and symptoms arising from tumor size.

Two principals behind the procedures can be identified: (1) ablative therapies, such as radiofrequency ablation (RFA) or laser interstitial thermotherapy (LITT); and (2) transarterial approaches, such as transarterial embolization (TAE), transarterial chemoembolization (TACE) and selective intraarterial radiotherapy (SIRT).

Ablative strategies can be used in oligonodular, bilobular liver metastases. These procedures are limited if the metastasis is localized in the vicinity of a liver vein or portal vein, as this leads to a temperature steal phenomenon, lowering the heat in the metastasis needed to ablate the lesion. Furthermore, RFA can be applied in combination with liver resections (in the same setting), or percutaneously with CT-guidance. Henn *et al*[41] treated up to 12 lesions in one RFA setting under CT-guidance with a maximum lesion size of 7.1 cm. Other groups reported successful treatment of lesions with a maximum size of 9 cm[42]. Complications of RFA have mostly been related to electrode application, such as pneumothorax and neuritis at the site of skin entry. Other complications include skin burn, liver abscess and transient elevation of liver enzymes[43].

Laser interstitial thermotherapy (LITT) is a thermal ablation technique that uses a ND-YAG laser, which transports its energy *via* a cannulation needle and a special protective catheter system to the liver metastases. The

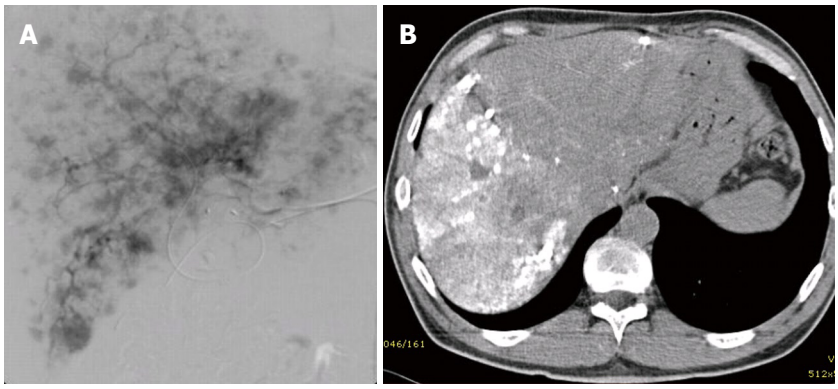


Figure 3 Diffuse liver metastases of a non-functional pancreatic endocrine tumors. Angiography (A) and chemoembolization of the right liver lobe (B).

advantage of this laser application system is that it can be performed under MR-guidance. Furthermore, the efficacy of this procedure can be simultaneously evaluated under MRI[44]. Complications arising from this procedure are similar to those of RFA, being liver enzyme elevation, pleural effusion and subcapsular hematomas.

Loco-regional transarterial therapy procedures can further be subdivided into transarterial embolization (TAE) and transarterial chemoembolization (TACE). The rationale behind these endovascular procedures is the fact that neuroendocrine tumors produce highly vascular metastases in the liver, and those metastases draw their blood supply predominantly (> 90%) from the hepatic artery, rather than the surrounding liver tissue, which receives only 20%-30% of its supply from the hepatic artery, but 70%-80% from the portal vein[43]. In TAE, embolization is performed using lipiodol, gel foam particles, polyvinyl alcohol foam (PVA) and microspheres[45]. As the tumor-supplying artery can be superselectively embolized, the effect of devascularization can be achieved more effectively with a lower possibility of collateral supply, in comparison to surgical ligation. Another advantage of TAE and TACE is that in case of recurrence or revascularization, the procedure can be repeated.

TACE follows the same principles as those of TAE, but an intra-arterial administration of a chemotherapeutic agent is added, prior to the embolization procedure (Figure 3). The advantage of this technique is the synergistic effect of chemotherapy, which has a more than 20 times higher intra-tumoral concentration when compared to a systemic administration, and the effect of tumor ischemia due to embolization[46]. The chemotherapeutic agents and the embolization particles used vary between the different groups and publications, but doxorubicin and streptozocin have mostly been used.

The symptomatic response rate, by which is meant the improvement of symptoms of hormonal syndromes, is estimated for TAE in 64%-93% of patients in a time period of 1-18 mo. TACE is associated with a symptomatic response in between 53%-95% of patients for a period of 1-55 mo[43]. Complications of TAE and TACE vary in the literature. 80%-90% of all patients experience fever, leukocytosis, abdominal pain and liver enzyme elevation. More severe complications range from pleural effusion, liver abscess, bowel ischemia to hepatic infarction.

Selective intra-arterial radiotherapy (SIRT) provides a selective, loco-regional radiotherapy of the liver metastases. In this procedure, ^{90}Y-DOTA-lantreotide is applied directly to the metastases using an interventional approach, and is targeted to the somatostatin receptors expressed by the metastases. The metastases usually express somatostatin receptors 2-5, but the expression has to be verified prior to this procedure using somatostatin-receptor-scintigraphy or ^{18}Fluordesoxyglucose-(DOTA(0)-Phe(1)-Tyr(3) octreotid-PET[47].

CONCLUSION

Neuroendocrine tumors are uncommon but clinically challenging and fascinating tumors with an annual incidence of 1 per 100 000 people. They present either as functional tumors or as non-functional pancreatic tumors. The natural history of NPTs is highly variable. Small, benign neoplasms, such as 90% of all insulinomas, are readily curable by surgical resection; however, most other functional and all non-functional pancreatic tumors have a much less favorable prognosis. The existence or development of liver metastases is the worst prognostic factor. This review describes the current status of surgical, interventional and medical treatment of liver metastases for pancreatic endocrine tumors, and discusses the new developments in this field.

REFERENCES

1 **Metz DC**, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology* 2008; **135**: 1469-1492
2 **Öberg K**, Eriksson B. Endocrine tumors of the pancreas. *Best Pract Res Clin Gastroenterol* 2005; **19**: 753-781
3 **Fendrich V**, Waldmann J, Bartsch DK, Langer P. Surgical management of pancreatic endocrine tumors. *Nat Rev Clin Oncol* 2009; **6**: 419-428
4 **Danforth DNJ**. Metastatic insulin-secreting carcinoma of the pancreas: clinical course and the role of surgery. *Surgery* 1984; **96**: 1027–1036
5 **Weber HC**. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. *Gastroenterology* 1995; **108**: 1637-1649
6 **Yu F**. Prospective study of the clinical course, prognostic factors, causes of death, and survival in patients with long-standing Zollinger-Ellison syndrome. *J Clin Oncol* 1999; **17**: 615-630

7 **Hochwald S**. Prognostic factors in pancreatic endocrine neoplasms: an analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. *J Clin Oncol* 2002; **20**: 2633-2642
8 **Bartsch DK**. Outcome of duodenopancreatic resections in patients with multiple endocrine neoplasia type 1. *Ann Surg* 2005; **242**: 757-766
9 **Doherty GM**. Lethality of multiple endocrine neoplasia type I. *World J Surg* 1998; **22**: 581-587
10 **Halfdanarson TR**. Pancreatic endocrine neoplasms: epidemiology and prognosis of pancreatic endocrine tumors. *Endocr Relat Cancer* 2008; **15**: 409-427
11 **Fendrich V**. An aggressive surgical approach leads to long-term survival in patients with pancreatic endocrine tumors. *Ann Surg* 2006; **244**: 845-851
12 **Lo CY**. Islet cell carcinoma of the pancreas. *World J Surg* 1996; **20**: 878-883
13 **Sarmiento JM**, Que FG, Grant CS. Concurrent resections of pancreatic islet cell cancers with synchronous hepatic metastases: outcomes of an aggressive approach. *Surgery* 2002; **132**: 976-983
14 **Evans DB**. Nonfunctioning islet cell carcinoma of the pancreas. *Surgery* 1993; **114**: 1175–1182
15 **Solorzano CC**. Nonfunctioning islet all carcinoma of the pancreas: survival results in a contemporary series of 163 patients. *Surgery* 2001; **130**: 1078–1085
16 **Touzios JG**. Neuroendocrine hepatic metastases: does aggressive management improve survival? *Ann Surg* 2005; **241**: 776-785
17 **Dousset B**. Metastatic endocrine tumors: medical treatment, surgical resection, or liver transplantation. *World J Surg* 1996; **20**: 908-914
18 **Que FG**. Hepatic resection for metastatic neuroendocrine carcinomas. *Am J Surg* 1995; **169**: 36-42
19 **Chen H**. Isolated liver metastases from neuroendocrine tumors: does resection prolong survival? *J Am Coll Surg* 1998; **187**: 188-192
20 **Chamberlain RS**. Hepatic neuroendocrine metastases: does intervention alter outcomes? *J Am Coll Surg* 2000; **190**: 432-435
21 **Nave H**. Surgery as primary treatment in patients with liver metastases from carcinoid tumors: a retrospective, unicentric study over 13 years. *Surgery* 2001; **129**: 170-175
22 **Sarmiento JM**. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. *J Am Coll Surg* 2003; **197**: 29-37
23 **Moertel CG**. An odyssey in the land of small tumors. *J Clin Oncol* 1987; **5**: 1503-1522
24 **Que FG**. Hepatic surgery for metastatic gastrointestinal neuroendocrine tumors. *Cancer Control* 2002; **9**: 67-79
25 **Pascher A**. Transplantation in the management of metastatic endocrine tumours. *Best Pract Res Clin Gastroenterol* 2005; **19**: 637-648
26 **Rosenau J**. Ki67, E-cadherin, and p53 as prognostic indicators of long-term outcome after liver transplantation for metastatic neuroendocrine tumours. *Transplantation* 2002; **73**: 386–394
27 **Faiss S**, Pape UF, Bohmig M, Dorffel Y, Mansmann U, Golder W, Riecken EO, Wiedenmann B. Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors--the International Lanreotide and Interferon Alfa Study Group. *J Clin Oncol* 2003; **21**: 2689-2696
28 **Plockinger U**, Rindi G, Arnold R, Eriksson B, Krenning EP, de Herder WW, Goede A, Caplin M, Oberg K, Reubi JC, Nilsson O, Delle FG, Ruszniewski P, Ahlman H, Wiedenmann B. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). *Neuroendocrinology* 2004; **80**: 394-424
29 **Rinke A**, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, Mayer C, Aminossadati B, Pape UF, Blaker M, Harder J, Arnold C, Gress T, Arnold R. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol* 2009; **27**: 4656-4663
30 **Ruszniewski P**, Ish-Shalom S, Wymenga M, O'Toole D, Arnold R, Tomassetti P, Bax N, Caplin M, Eriksson B, Glaser B, Ducreux M, Lombard-Bohas C, de Herder WW, Delle FG, Reed N, Seitz JF, Van CE, Grossman A, Rougier P, Schmidt W, Wiedenmann B. Rapid and sustained relief from the symptoms of carcinoid syndrome: results from an open 6-month study of the 28-day prolonged-release formulation of lanreotide. *Neuroendocrinology* 2004; **80**: 244-251
31 **Tomassetti P**, Migliori M, Corinaldesi R, Gullo L. Treatment of gastroenteropancreatic neuroendocrine tumours with octreotide LAR. *Aliment Pharmacol Ther* 2000; **14**: 557-560
32 **Oberg K**, Ferone D, Kaltsas G, Knigge UP, Taal B, Plockinger U. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: biotherapy. *Neuroendocrinology* 2009; **90**: 209-213
33 **Kouvaraki MA**, Ajani JA, Hoff P, Wolff R, Evans DB, Lozano R, Yao JC. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol* 2004; **22**: 4762-4771
34 **Moertel CG**, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *N Engl J Med* 1992; **326**: 519-523
35 **Moertel CG**, Kvols LK, O'Connell MJ, Rubin J. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer* 1991; **68**: 227-232
36 **Maire F**, Hammel P, Faivre S, Hentic O, Yapur L, Larroque B, Couvelard A, Zappa M, Raymond E, Levy P, Ruszniewski P. Temozolomide: a safe and effective treatment for malignant digestive endocrine tumors. *Neuroendocrinology* 2009; **90**: 67-72
37 **Varker KA**, Campbell J, Shah MH. Phase II study of thalidomide in patients with metastatic carcinoid and islet cell tumors. Cancer Chemother. *Pharmacol* 2008; **61**: 661-668
38 **Raymond E**, Faivre S, Hammel P, Ruszniewski P. Sunitinib paves the way for targeted therapies in neuroendocrine tumors. *Target Oncol* 2009; **4**: 253-254
39 **Yao JC**, Lombard-Bohas C, Baudin E, Kvols LK, Rougier P, Ruszniewski P, Hoosen S, St PJ, Haas T, Lebwohl D, Van CE, Kulke MH, Hobday TJ, O'Dorisio TM, Shah MH, Cadiot G, Luppi G, Posey JA, Wiedenmann B. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. *J Clin Oncol* 2010; **28**: 69-76
40 **Forrer F**, Valkema R, Kwekkeboom DJ, de JM, Krenning EP. Neuroendocrine tumors. Peptide receptor radionuclide therapy. *Best Pract Res Clin Endocrinol Metab* 2007; **21**: 111-129
41 **Henn AR**, Levine EA, McNulty. Percutaneous radiofrequency ablation of hepatic metastases for symptomatic relief of neuroendocrine syndromes. *Am J Roentgenol* 2003; **181**:1005-1010
42 **Gilliams A**, Cassoni A, Conway G. Radiofrequency ablation of neuroendocrine liver metastases: the Middlesex experience. *Abdom Imaging* 2005; **30**: 435-441
43 **Vogl TJ**, Naguib NN, Zangos S. Liver metastases of neuroendocrine carcinomas: Interventional treatment via transarterial embolization chemoembolization and thermal ablation. *Eur J Radiol* 2005; **72**: 517-528
44 **Vogl TJ**, Mack MG, Balzer JO. Liver metastases: neoadjuvant downsizing with transhepaticarterial chemoembolization before laser induced thermotherapy. *Radiology* 2003; **229**: 427-434

45 **Gupta S**, Johnson MM, Murthy R. Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumors: variables affecting response rate and survival. *Cancer* 2005; **104**: 1590-1602
46 **Roche A**, Girish BV, de Baere T. Trans-catheter arterial cheoembolization as first line treatment for hepatic metastases from neuroendocrine tumors. *Eur Radiol* 2003; **13**: 136-140
47 **McStay MK**, Maudgil D, Williams M. Large volume liver metastases from neuroendocrine tumors hepatic intra arterial 90Y-DOTA-Lantreotide as effective therapy. *Radiology* 2005; **237**: 718-726

S- Editor Zhang HN **L- Editor** Herholdt A **E- Editor** Liu N

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v2.i10.374

World J Hepatol 2010 October 27; 2(10): 374-383
ISSN 1948-5182 (online)

REVIEW

Current status and agenda in the diagnosis of nonalcoholic steatohepatitis in Japan

Yoshio Sumida, Yuichiro Eguchi, Masafumi Ono

Yoshio Sumida, Center for Digestive and Liver Diseases, Nara City Hospital, Nara 6308305, Japan
Yuichiro Eguchi, Department of General Medicine, Saga Medical School, Saga University, Saga 8498501, Japan
Masafumi Ono, Department of Gastroenterology and Hepatology, Kochi Medical School, Kochi 7838505, Japan
Author contributions: Eguchi Y and Ono M equally contributed to this work; and Sumida Y wrote the manuscript.
Correspondence to: Yoshio Sumida, MD, PhD, Center for Digestive and Liver Diseases, Nara City Hospital, Higashi Kidera-cho1-50-1, Nara 6308305, Japan. sumida@nara-jadecom.jp
Telephone: +81-742-241251 Fax: +81-742-222478
Received: June 21, 2010 Revised: September 22, 2010
Accepted: September 29, 2010
Published online: October 27, 2010

Abstract

Nonalcoholic fatty liver disease (NAFLD), a manifestation of metabolic syndrome, includes a wide range of clinical entities from simple fatty liver, a benign condition, to nonalcoholic steatohepatitis (NASH), a condition which can progress to cirrhosis, hepatocellular carcinoma and hepatic failure. The diagnosis of NASH requires no history of previous or current significant alcohol consumption and no evidence of other chronic liver diseases. Ethanol intake levels of 20 g daily (or 140 g weekly) are endorsed as the acceptable threshold to define no nalcoholic patients. Liver biopsy is the current gold stan dard for the diagnosis of NASH and provides progno stic information. Histopathological diagnosis of NASH is based on the following 3 features: (1) hepatic macrovesicular steatosis; (2) lobular inflammation; and (3) ballooning degeneration of hepatocytes. It is impractical to biopsy every patient with suspected NAFLD. Although highly accurate and affordable noninvasive screening tools can differentiate NASH from NAFLD, no imaging studies or laboratory tests are able to precisely diagnose NASH. There is no universal agreement regarding the indications for liver biopsy in NAFLD patients. In Japan, liver biopsies are considered in patients with suspected NAFLD based on several criteria including low platelet counts, elevated fibrosis markers, increasing age and other deciding parameters. Further studies are needed to establish a suitable scoring system that can distinguish steatohepatitis from simple steatosis.

Key words: Insulin resistance; Liver biopsy; Oxidative stress; Fibrosis

Peer reviewers: Amedeo Lonardo, MD, Internal Medicine, Endocrinology, Metabolism and Geriatrics, University of Modena and Reggio Emilia, Modena 41100, Italy; Norberto Carlos Chavez-Tapia, MD, PhD, Departments of Biomedical Research, Gastroenterology & Liver Unit, Medica Sur Clinic & Foundation, Puente de Piedra 150, Col. Toriello Guerra, Tlalpan 14050, Mexico City, Mexico

Sumida Y, Eguchi Y, Ono M. Current status and agenda in the diagnosis of nonalcoholic steatohepatitis in Japan. *World J Hepatol* 2010; 2(10): 374-383 Available from: URL: http://www.wjgnet.com/1948-5182/full/v2/i10/374.htm DOI: http://dx.doi.org/10.4254/wjh.v2.i10.374

INTRODUCTION

In 1980, Ludwig *et al*[1] coined the term nonalcoholic steatohepatitis (NASH) to describe the morphologic pattern of liver injury in 20 patients evaluated at the Mayo Clinic. These patients had histological evidence of alcoholic hepatitis on liver biopsy but no history of alcohol abuse. Nonalcoholic fatty liver disease (NAFLD) represents a wide spectrum of conditions ranging from simple fatty liver which in general follows a benign non-progressive clinical course to NASH, a more serious form of NAFLD that may progress to cirrhosis and end-stage liver disease[2]. NAFLD is strongly associated with obesity and metabolic syndrome. Today, NAFLD is the most common chronic liver disease (CLD) in the Western world[3,4] and in the

Asia-Pacific Region[5,6]. Although the true prevalence of NAFLD or NASH remains to be established, current best estimates make the prevalence of NAFLD 9%-30% and of NASH 1%-3% in Japan[7]. On imaging findings consistent with steatosis, a diagnosis of NAFLD can be made with a reasonable degree of confidence if a history of significant alcohol consumption and other causes of liver disease are excluded. Until recently, liver biopsy was the only method for differentiating NASH from simple fatty liver. This review paper discusses the clinical features and diagnostic challenges for NASH in Japan.

LABORATORY STUDIES/IMAGING

Liver transaminase levels are mildly elevated (usually < 3-5 x the upper limit of normal) in NASH patients. Although aminotransferase levels are elevated in the majority of patients, normal values do not exclude the presence of necroinflammatory changes or fibrosis[8-10]. The ratio of aspartate aminotransferase (AST) to alanine aminotransferase (ALT) is usually < 1 but this ratio increases as the level of fibrosis progresses[11-13]. Serum alkaline phosphatase (ALP) and γ-glutamyl transferase (γGT) may also be mildly elevated. Other abnormalities including hypoalbuminemia, a prolonged prothrombin time and hyperbilirubinemia may also be found in patients with cirrhotic-stage NASH. Increased serum ferritin levels are often seen in NASH patients but transferrin saturation is almost normal[14]. Although markers of insulin resistance and hepatic fibrosis seem to be higher in NASH than in simple fatty liver, currently laboratory studies cannot truly confirm a diagnosis of NASH.

Imaging tests [such as ultrasound (US), computed tomography (CT) or magnetic resonance imaging] may reveal fat accumulation in the liver but their sensitivity is low. Furthermore, these imaging studies cannot differentiate NASH from simple fatty liver[15]. Although US is an acceptable first-line screening procedure for NAFLD in clinical practice, it underestimates the prevalence of hepatic steatosis when there is < 20%-30% fat[15,16]. According to a study from Japan[17], US could more accurately identify the presence of steatosis in NASH patients than CT but the sensitivity of US for detecting steatosis was reduced, especially in patients with advanced histological fibrosis. Although other modalities such as transient elastography (Fibroscan, EchoSens, Paris, France), contrast enhanced US and Xenon CT are reported to be promising for distinguishing between simple fatty liver and NASH, there are no established noninvasive methods of evaluation available for patients with NAFLD. In Japan, contrast enhanced US with Levovist (Schering AG, Berlin, Germany) can identify patients with NASH among those with NAFLD[18,19]. Yoneda *et al* recently reported that elastography techniques such as transient elastography and acoustic radiation force impulse elastography have been shown to be useful for estimating liver fibrosis in NAFLD patients[20,21]. With high negative predictive value and modest positive predictive value in French and Chinese cohort of NAFLD patients[22], transient elastography is useful as a screening test to exclude advanced fibrosis. Although these techniques are painless, rapid, have no associated complications and are, therefore, very easily accepted by patients compared to liver biopsy, it may be difficult to distinguish between simple fatty liver and NASH with mild fibrosis.

DIFFERENTIAL DIAGNOSIS

A complete laboratory evaluation to exclude other causes of liver disease should also be performed. This includes screening for common causes such as viral hepatitis B and hepatitis C virus (HCV) as well as less common causes including autoimmune disorders, celiac disease and genetic conditions such as Wilson's disease, hemochromatosis and alpha-1-antitrypsin deficiency. Other liver diseases, hepatic malignancies, hepatobiliary infections and biliary tract disease should also be excluded[4,5]. Thus, hepatitis B surface antigen, anti-HCV, anti-nuclear antibody (ANA) and anti-mitochondrial antibodies (AMA) should be measured to rule out these diseases. Elevated serum autoantibodies are common in patients with NASH/NAFLD. Although low titers of ANA positivity are seen in up to a third of patients with NASH/NAFLD, ANA titers greater than 1:320 are generally rare. Therefore, ANA positivity does not always exclude NASH/ NAFLD[23-25]. Low titers of anti-smooth muscle antibody (ASMA) and AMA have also been reported in patients with NASH/ NAFLD[16,18]. In patients with suspected NAFLD, if ANA or ASMA titers are greater than 1:160 and 1:40 respectively, a liver biopsy should be considered to exclude the presence of autoimmune hepatitis[26]. Among NAFLD patients with ANA positivity, potential risk factors such as female sex, obesity, insulin resistance and severe fibrosis have been found in some studies although no consensus has been established. Familial hypobetalipoproteinemia (FHBL), a hereditary disorder characterized by decreased plasma concentrations of low-density lipoprotein (LDL) cholesterol and apolipoprotein B (Apo-B), is classified as one of the causes of NAFLD[27,28]. Regarding lipids, it is worth measuring serum levels of Apo-B in patients with no obvious risk factors for NAFLD or with low levels of LDL and HDL cholesterol to look for evidence of FHBL. In Japan, a case of FHBL with cryptogenic cirrhosis showing recurrent NASH after undergoing living donor liver transplantation was reported[29].

Due to its high prevalence, it is now recognized that NAFLD/NASH can occur together with other CLDs. In chronic hepatitis C, and possibly ALD and hemochromatosis, NAFLD can exacerbate liver damage[30-32]. The diagnosis and management of NAFLD with other CLDs remains unresolved. The nomenclature "NASH" may be changed for these reasons as proposed by Brunt[33]. This strongly argues for a change in nomenclature (such as metabolic fatty liver disease and metabolic steatohepatitis) which would drop the "negative" definition of "non-alcoholic" and would recognize the likely causal role of insulin resistance in NAFLD/NASH.

MEANING OF "NONALCOHOLIC" LIVER DISEASE

The diagnosis of NASH requires no history of significant alcohol consumption. There is no consistent agreement regarding the definition of significant alcohol consumption. According to the Italian Association for the Study of the Liver Expert Committee[34] and the position statement on NAFLD/NASH based on the European Association for the Study of the Liver (EASL) 2009 special conference[35], European hepatologists suggested a daily alcohol consumption 20 g in women and 30 g in men as the optimal cutoff values of "non-alcoholic". According to the American Gastroenterological Association (AGA) institute technical review on nonalcoholic fatty liver disease[3] and the summary by the American Association for the Study of Liver Diseases (AASLD)[4], a daily alcohol consumption of > 20 g/d is commonly used as exclusionary criteria; however, the validity of these cutoffs is unknown. In contrast, intake levels of 20 g/d (140 g weekly) for men, and 10 g/d (70 g weekly) for women have been endorsed as the acceptable thresholds to define "non-alcoholic" in the guideline proposed by the Asia-Pacific Working Party for NAFLD (APWP-NAFLD)[5] and by the National Institutes of Health Clinical Research Network[36]. The reason that a small amount of alcohol intake is permitted in the diagnosis of NASH is based on the fact that intake levels above the defined thresholds (> 20 to 40 g/d in males and > 10-30 g/d in females) are toxic for the liver[37-39] and because modest alcohol consumption is thought to reduce the prevalence of NAFLD by improving insulin resistance[40-42]. At the 45th Annual Meeting of the Japan Society of Hepatology (JSH) in June 2009, a consensus was reached that alcohol intake levels of 20 g/d (140 g/wk) were accepted as the optimal cut-off values of "non-alcoholic"[43]. It is often difficult to differentiate NASH from ALD. Conventional markers such as mean corpuscular volume, γGT and AST/ALT ratio are not useful and specific serum markers for chronic alcohol abuse are of limited value. Measurement of carbohydrate-deficient transferrin levels (CDT) is the most widely used and perhaps the most specific serum marker for detecting chronic alcohol abuse. Serum CDT levels were known to be lower in patients with alcoholic hepatitis than those with NASH[44]. Practical clinical use of this marker is questionable because it can be measured only in research laboratories. A careful history of alcohol intake is essential to exclude alcohol-induced fatty liver disease (AFLD) because the histological features of AFLD and NAFLD are indistinguishable for pathologists. It is difficult to distinguish between these two entities, especially in those with obesity and associated metabolic risk factors because AFLD and NAFLD commonly occur in this population. The diagnosis and treatment of this condition is still unclear.

HISTOLOGICAL DIAGNOSIS

Currently, histological assessment of liver biopsy specimens remains the gold standard for the diagnosis of NAFLD. There are a constellation of histological findings in NASH with no single pathognomonic lesion. The principal histological features of NASH include the presence of macrovesicular fatty changes of hepatocytes with displacement of the nucleus to the edge of the cell, ballooning degeneration of hepatocytes and a mixed lobular inflammation. Other features such as perisinusoidal/peri-cellular fibrosis, Mallory-Denk bodies (MDB), megamitochondria, acidophil bodies, glycogenated nuclei and hemosiderosis can be found. Bridging fibrosis and cirrhotic changes may be present in the advanced fibrotic stage. In spite of considerable efforts, there is still no international agreement regarding the histopathological criteria that firmly define NASH. Therefore, a large amount of uncertainty exists between pathologists and clinicians. Moreover, borderline lesions of the two entities exist in clinical practice. In 1999, Matteoni *et al*[45] divided NAFLD into four categories or types based on the presence of steatosis, lobular inflammation, hepatocyte ballooning and MDB/fibrosis (Table 1). As originally reported, after a median follow-up period of 8.17 years, liver-related mortality of NALD (type 3 or 4) was 11% versus 1.7% in NAFLD (type 1 or 2)[46]. A more recent study with a median follow-up period of 18.5 years showed that liver-related mortality of NALD (type 3 or 4) increased to 17.5% in comparison with only 2.7% in NALD (type 1 or 2)[32]. NAFLD (type 3 or 4) is now considered to be a single group that represents NASH[47]. These findings confirm that, with longer follow-up periods, more NASH patients develop liver-related deaths. It also confirms that most patients with non-NASH are not at similar risk of liver-related deaths. Long term follow-up studies have never been performed in Japanese patients with NAFLD. It is expected that prospective studies in Japan will confirm these observations. On the basis of this classification system, hepatocyte ballooning should be considered as a more specific histological feature for the diagnosis of NASH. However, the presence or absence of hepatocyte ballooning is influenced by the var iability in pathologists' interpretation. To account for this, another scoring system has been developed by the Na tional Institute of Diabetes and Digestive and Kidney Diseases. The score, named NAS (NAFLD Activity Score), is the unweighted sum of the scores for steatosis (0-3), lobular inflammation (0-3) and ballooning (0-2). NAS does not include fibrosis (Table 1). A NAS of ⩾ 5 is almost always associated with the diagnosis of NASH and cases with a NAS of < 3 are largely considered to be "non-NASH". Patients who had scores of 3 or 4 are reported to be borderline[33]. The system is simple and requires only routine histochemical stains with reasonable inter-observer reproducibility. This score is valuable for quantifying histological changes, especially in clinical trials, but its generalizability and diagnostic utility are unknown. Clinically important differences exist between community general pathologists and expert hepatopathologists in assessing NAS[48]. The primary purpose of NAS is to assess overall histological change; it was not designed to replace

Table 1 The pathological criteria for the diagnosis of nonalcoholic fatty liver disease

Matteoni's classification[45]				
Type	Histological findings	Liver related deaths (mean observation period) 8.17 years[31]	18.5 years[32]	Diagnosis
Type 1	Fatty liver alone	1.70%	2.70%	non-NASH
Type 2	Fat accumulation and lobular inflammation			
Type 3	Fat accumulation and ballooning degeneration	11.00%	17.50%	NASH
Type 4	Type 3 and either Mallory-Denk body or fibrosis			
NAFLD activity score (NAS)[47]				
Item	Definition		Score	Diagnosis
Steatosis	< 5%		0	Total score
	5%-33%		1	0-2: non-NASH
	> 33%-66%		2	3-4: borderline
	> 66%		3	5-8: NASH
Lobular inflammation	No foci		0	
	< 2 foci per 200 × field		1	
	2-4 foci per 200 × field		2	
	> 4 foci per 200 × field		3	
Ballooning	None		0	
	Few balloon cells		1	
	Many cells/prominent ballooning		2	

NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis.

the pathologist's determination of steatohepatitis or to represent an absolute severity scale. In some patients with cirrhosis, the features of steatosis and necroinflammatory activity may no longer be present (so called "burned-out NASH"). NAS has some limitations in diagnosing NASH in such patients. However, APWP-NAFLD suggests that use of NAS should be encouraged for routine reporting as well as research studies[5]. At the 45th Annual Meeting of the JSH in June 2009, it was agreed that a diagnosis of NASH should be based on the following three features: (1) hepatic steatosis (> 5%-10% of hepatocytes affected); (2) lobular inflammation with mononuclear cells and/or neutrophils; and (3) ballooning degeneration of hepatocytes[43]. The presence of fibrosis or MDB is not essential for a diagnosis of NASH[4,5,43]. A universally accepted histological grading and staging system for steatohepatitis does not exist. The first histological scoring system for NASH was proposed by Brunt *et al*[49]; its design was based on a model used in other CLDs and included three qualitatively assessed grades of necroinflammatory activity (based on degrees of steatosis, ballooning and inflammation) and four stages of fibrosis. Unfortunately, this system applied only to NASH and it is not applicable to the entire spectrum of NAFLD.

INDICATIONS AND LIMITATIONS OF LIVER BIOPSY

Liver biopsy remains the best diagnostic tool for confirming NASH as well as the most sensitive and specific means of providing important prognostic information. Liver biopsy is also helpful to determine the effect of medical treatment given that there is poor correlation between histological damage and the results of liver tests or imaging studies. However, it is not practical to biopsy every patient with suspected NAFLD. The AGA states that the decision to perform a liver biopsy in a patient with suspected NAFLD and the timing of the biopsy must be individualized and should include the patient in the decision making process[3]. According to the AASLD, firm recommendations of when to perform a liver biopsy in the routine clinical setting have not yet been developed and management decisions will continue to be tailored to individual patients[4]. According to APWP-NAFLD[5], liver biopsy is not usually required for diagnosis of NAFLD. However, it should be considered in cases where: (1) there is diagnostic uncertainty; (2) patients are at risk of advanced hepatic fibrosis (in the absence of clinical or imaging evidence of cirrhosis); (3) in those enrolled in clinical trials; and (4) because of reduced risk and grea ter convenience in those already undergoing laparoscopy for another purpose (e.g. cholecystectomy, gastric banding). Based on the EASL 2009 special conference[35], liver biopsy may be restricted to cases where non-invasive methods suggest advanced fibrosis and to cases with indeterminate or discordant results, thus deemed insufficient to exclude advanced fibrosis. During elective surgical procedures such as bariatric surgery and cholecystectomy, they suggest that a liver biopsy be performed. At the 45th Annual Meeting of the JSH in June 2009, it was agreed that liver biopsies are considered in patients with suspected NAFLD based on several criteria including low platelet counts, elevated hepatic fibrosis markers, increasing age and other deciding parameters. However, the optimal cut-off values of these parameters have never been established[43]. In this way, no guidelines or firm recommendations have yet been made as to when and for whom it is necessary. Arguments against routine liver biopsy include the generally benign course of the disease in most cases, lack of established effective therapies and the risks of biopsy. As a single percutaneous liver biopsy yields only a minute percentage (1/50000 or 0.002%)

Table 2 Noninvasive biomarkers previously studied or currently under evaluation

Insulin resistance	**Inflammation and apoptosis**
HOMA-IR	TNF-α
Leptin	hsCRP
Adiponectin	CK-18 fragments
	TNF-α/adiponectin ratio
Hepatic fibrosis	Interleukin-6
Hyaluronic acid	CC-chemokine ligand-2
Type Ⅳ collagen 7S	
TGFβ	**Endocrine**
	DHEA-S
Oxidative stress	
Ferritin	**Imaging studies**
TBARS	US elastography
Oxidized-LDL	Fibroscan
Total antioxidant response	ARFI
Total lipid peroxide levels	Contrast enhanced US
Thioredoxin	MRI (SPIO, Gd-EOB-DTPA)
Advanced glycation end products	

HOMA-IR: homeostasis model assessment for insulin resistance; TGFβ: transforming growth factor β; TBARS: thiobarbituric acid-reacting substance; LDL: low-density lipoprotein; TNF: tumor necrosis factor; hsCRP: high sensitivity C-reactive protein; CK: cytokeratin; CCL2: CC-chemokine ligand-2; DHEA-S: dehydroepiandrosterone-sulphate; ARFI: acoustic radiation force impulse elastography; SPIO: super-paramagnetic iron oxide; US: ultrasound; MRI: magnetic resonance imaging.

of the total hepatic tissue, paired biopsies have been evaluated in several published studies. Several recent studies have highlighted its sampling variability, although this may be attenuated with good core biopsy samples[50,51]. According to two studies[52,53], a difference of one stage of fibrosis or more was seen in 30%-41% of paired biopsies. In contrast, recent data have shown that significant sampling variability exists for inflammatory changes rather than steatosis or fibrosis[54]. In addition to the sampling variability noted above, variability in pathologists' interpretation also exists for liver inflammation compared to steatosis or fibrosis[54,55]. It is obvious that liver biopsy is an invasive procedure, stressful for patients and their physicians and is associated with potential significant complications such as pain, hemorrhage and so on[26,56,57]. Finally, another important limitation of liver biopsy relates to the fact that histological analysis remains subjective, influenced by the skill and experience of the examining pathologist. Overall, a large amount of confusion continues to exist between pathologists and clinicians for this condition.

NONINVASIVE TESTS FOR DISTINGUISHING NASH FROM NAFLD

Currently, liver biopsy is the gold standard for diagnosis but there is an increasing requirement for simple, less invasive, highly accurate and affordable screening tools. Moreover, given the extremely high prevalence of NAFLD in the general population, a liver biopsy is poorly suited as a diagnostic test for NAFLD. A variety of clinical parameters, indicators of insulin resistance, oxidative stress[58], inflammation, fibrosis, apoptosis and endocrine function have been explored to distinguish between simple fatty liver and NASH (Table 2). As we previously reported, thioredoxin (TRX), an oxidative stress-inducible thiol-containing protein which has important roles in redox regulation, is also significantly elevated in the NASH patients' serum compared to those with simple fatty liver or healthy subjects[59]. Advanced glycation end products (AGEs), final reaction products of protein with sugars, are elevated in NASH patients compared to simple steatosis or healthy people[60] and are decreased after the treatment with atorvastatin[61]. Dehydroepiandrosterone (DHEA), the most abundant steroid hormone, has been shown to influence sensitivity to reactive oxygen species, insulin sensitivity and expression of peroxisome proliferator-activated receptor alpha. Low levels of circulating sulfated-DHEA (DHEA-S) might have a role in the development of advanced NASH[62]. This was confirmed by our validation study using a Japanese population with NAFLD[63]. Elevation of serum ferritin levels, a marker of iron storage, is associated with NASH. We previously reported high frequencies of hyperferritinemia and increased hepatic iron stores in Japanese NASH patients[59]. Yoneda *et al*[64] also have reported that measurement of serum ferritin is useful to distinguish NASH from NAFLD. In the Japanese population, however, the frequency of HFE mutation (hemochromatosis gene) is known to be extremely rare. This mutation does not have a role in hepatic iron overload in Japanese NASH[65]. Serum ferritin levels have been found to be a significant independent predictor of severe fibrosis in 167 Italian NAFLD subjects[66] but this has not been confirmed by other studies. In Western countries, mildly increased serum ferritin does not necessarily indicate coexisting iron overload. Recently, it is noteworthy that serum ferritin is closely associated with insulin resistance and can be considered a marker for metabolic syndrome[67]. Elevated serum ferritin in NASH may be derived from multiple factors such as hepatic iron accumulation but also hepatic inflammation, highly expressed cytokines, oxidative stress and so on[14]. Apoptosis has an important role in the pathogenesis of NASH. Caspase generated cytokeratin 18 (CK-18), a protein in involved in apoptosis, is elevated in patients with NASH compared to those with simple fatty liver and normal subjects[68]. Also, in Japan, this marker is useful for assessing and monitoring the histological activity of NAFLD[69]. Kitade *et al*[70] reported that significant development of hepatic neovascularization was observed in NASH and CK-18 levels were also positively correlated with the degree of neovascularization. These provocative preliminary data deserve further study but it may be too optimistic to assume that a single biomarker can reliably predict histology in NAFLD, a condition with relatively complex phenotype and multiple comorbidities. Currently it is not routinely available as a laboratory test. These tests are inconclusive in many patients and have not been fully validated in patients with NAFLD.

In an effort to improve to accurately diagnose NASH

Table 3 Panel markers for nonalcoholic steatohepatitis diagnosis

Index	Author (Nation)	Paper	Parameter	Patient selection	*N*	AUROC
HAIR score	Dixon JB (Australia)	Gastroenterology 2001	HTN, ALT, insulin resistance (1/QUICKI)	patients with BMI > 35 undergoing laparoscopic banding	105	0.900
	Palekar NA (USA)	Liver Int 2006	Age, female, BMI, AST, AST/ALT ratio, HA	biopsy proven NAFLD	80	0.763
NashTest (NT)	Poynard T (France)	BMC Gastroenterol 2006	Age, sex, height, weight, TG, AST, ALT, TC, α2-macroglobulin, apolipoprotein A1, haptoglobin, γGT, T-Bil	biopsy proven NAFLD	257	0.790
	Gholam (USA)	Am J Gastroenterol 2007	AST, DM	Severely obese subjects (BMI ≥ 40 kg/m^2) undergoing Rouxen-Y gastric bypass surgery	97	0.820
NASH clinical scoring system	Campos GM (USA)	Hepatology 2008	HTN, DM, AST, ALT, sleep apnea, non-black	Patients undergoing laparoscopic banding	200	
NAFIC score	Sumida Y (Japan)	J Gastroenterol, in press	Ferritin, fasting insulin, type Ⅳ collagen 7S	Biopsy proven NAFLD	177[1] 442[2]	0.851[1] 0.782[2]

HA: hyaluronic acid; TG: triglyceride; TC: total cholesterol; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; HTN: hypertension; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BMI: body mass index; γGT: γ-glutamyl transferase; T-Bil: total bilirubin; DM: diabetes mellitus; AUROC: area under the receiver operating characteristic curve; [1]Estimation group; [2]Validation group.

Table 4 Panel markers for fibrosis in nonalcoholic fatty liver disease

Index	Author (Nation)	Paper	Parameter	Patient selection	*N*	Stage	AUROC
	Angulo P (USA)	Hepatology 1999	Obesity[1], age, AST/ALT ratio, DM	NASH	144	F0-2 *vs* F3-4	
BAAT	Ratziu V (France)	Gastroenterology 2000	BMI, age, ALT, TG	Patients with BMI>25, raised transaminse	93	F0-1 *vs* F2-4	0.840
FibroTest (FT)	Ratziu V (France)	BMC Gastroenterol 2006	Age, sex, α2-macroglobulin, , apolipoprotein A1, haptoglobin, T-Bil, γGT	Biopsy proven NAFLD	267	F0-2 *vs* F3-4	0.840
N score	Miyaaki H (Japan)	Liver Int 2008	Female, age, DM, HT	Biopsy proven NAFLD	182	F0-2 *vs* F3-4	0.780
NAFLD fibrosis score	Angulo P (USA, UK, Australia, Italy)	Hepatology 2007	Age, BMI, AST/ALT ratio, IFG/DM, platelet count, albumin	Biopsy proven NAFLD	480[2] 253[3]	F0-2 *vs* F3-4	0.880[2] 0.820[3]
ELF panel	Guha IN (UK)	Hepatology 2008	TIMP1, HA, P3NP	Biopsy proven NAFLD	192	F0 *vs* F1-4 F0-1 *vs* F2-4 F0-2 *vs* F3-4	0.820 0.900 0.930
BARD score	Harrison SA (USA)	Gut 2008	BMI, AST/ALT, DM	Biopsy proven NAFLD	827	F0-2 *vs* F3-4	0.810[2] 0.780[3]
FIB4 index	Shah (USA)	Clin Gastroenterol Hepatol 2009	Age, AST, ALT, PLT	Biopsy proven NAFLD	541	F0-2 *vs* F3-4	0.802
FibroMeter	Calès (France)	J Hepatol 2009	Glucose , AST, ferritin, PLT, ALT, BW, age	Biopsy proven NAFLD	235	F0-1 *vs* F2-4	0.936[2] 0.952[3]
PAF	Hossain (USA)	Clin Gastroenterol Hepatol 2009	Male , Caucasian, DM, ALT, AST	Biopsy proven NAFLD	432	F0-1 *vs* F2-4	0.742

[1]BMI > 31.1 (male), 32.2 (female); [2]Estimation group; [3]Validation group; TG: triglyceride; IFG: impaired fasting glycemia; TIMP1: tissue inhibitor of metalloproteinases; HA: hyaluronic acid; P3NP: type Ⅲ procollagen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BMI: body mass index; PLT: platelets; γGT: γ-glutamyl transferase; T-Bil: total bilirubin; DM: diabetes mellitus; BW: body weight; AUROC: area under the receiver operating characteristic curve; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis.

noninvasively and determine the stage of fibrosis, several groups have used different combinations of clinical and biochemical markers to generate various clinical scoring systems. A proprietary algorithm that provides an estimate for either NASH diagnosis (Table 3) or the presence and extent of fibrosis (Table 4) have also been developed. It is uncertain whether these scoring systems will be useful for Asian/Japanese patients because almost all of the proposed scoring systems have been based on Western subjects and the definition of severely obese differs between the West and Japan. In fact, many previous studies have reported that "overweight" Asians who are not "morbidly obese" by Western standards generally have a higher risk of developing lifestyle related diseases such as metabolic syndrome, type 2 diabetes and fatty liver disease. Most noninvasive diagnostic tools for NASH are developed from studies using small sample sizes and also lack rigorous external validation. Although serological hepatic fibrosis markers such as hyaluronic acid[71] or type Ⅳ collagen 7S[72] are expected to be able to differentiate the advanced stage from mild fibrosis, there are no favorable serological markers to distinguish early stage NASH from simple steatosis without inflammation and fibrosis. In Japan, Shimada *et al*[73] suggested that

Table 5 NAFIC score[80]

Variables	Cut-off values	Score values
Ferritin (Female/Male) (ng/mL)	200/300	1 point
Insulin (μU/mL)	10.0	1 point
Type Ⅳ collagen 7S (ng/mL)	5.0	2 point

combinations of type Ⅳ collagen 7S, adiponectines and HOMA-IR are useful to distinguish early stage NASH from simple steatosis in Japanese NAFLD patients.

Recently, four new scoring systems have been described, the NAFLD fibrosis score[12], enhanced liver fibrosis score[74], BARD score[13] and FIB-4 index[75]; all are based on relatively large sample sizes and show encouraging results. However, according to a study of 122 Japanese NAFLD patients by Fujii *et al*[76], when a BARD score of 2 or more was used, the area under the receiver operating characteristic curve (AUROC) was 0.73 with an odds ratio (OR) of 4.9 for the detection of advanced fibrosis. It was concluded that the BARD score is less predictive of advanced fibrosis in Japanese NAFLD patients, mainly because they are not as obese as in Western countries. In Japan, Fujii *et al* showed that noninvasive laboratory tests designed to predict cirrhosis in patients with HCV such as AST/ALT ratio, age-platelet index, AST-to-platelet ratio index, cirrhosis discriminant score and the hepatitis C antiviral long-term treatment against cirrhosis model are also useful in patients with NASH[77]. The N score (the total number of the following risk factors: female > 60 years, type 2 diabetes and hypertension), established on the basis of a multicentre study of 182 Japanese NAFLD patients in Nagasaki[78], is very simple tool to use in practice. These promising models will need to be validated by external investigators before they are recommended for wide clinical use. However, the question is what stage of disease should be distinguished by using these parameters or scoring systems[79]. The majority of studies concentrate on the distinction of severe fibrosis but separation of the milder forms of fibrosis and NASH from simple steatosis is required to support emerging therapeutic trials. We have, therefore, constructed a simple clinical scoring system of three variables; serum ferritin, fasting insulin and type Ⅳ collagen 7S, based on the multiple regression analysis on data from 177 biopsy-proven Japanese NAFLD. These three variables were combined in a weighted sum [serum ferritin ⩾ 200 ng/mL (female) or 300 ng/mL (male) = 1 point, fasting insulin ⩾ 10 lU/mL = 1 point and type Ⅳ collagen 7S ⩾ 5.0 ng/mL = 2 points] to form an easily cal culated composite score for predicting NASH, called the NAFIC score (Table 5). According to our validation study of 442 Japanese patients with biopsy-proven NAFLD from the Japan Study Group of NAFLD (JSG-NAFLD) including eight hepatology centers in Japan, AUROC was the greatest for NAFIC score among several previously established scoring systems for detecting NASH but also for predicting significant or severe fibrosis[80]. Our results suggest that liver biopsies can be avoided in NAFLD patients with a NAFIC score of 0 or 1 because they are likely to have NAFLD without advanced fibrosis. In contrast, liver biopsies should be recommended in NAFLD patients with an NAFIC score of ⩾ 2 to assess the extent of hepatic fibrosis and predict prognosis. Thus, the diagnostic algorithm for NASH diagnosis in Japan proposed by JSG-NAFLD is shown in Figure 1. The present results need to be validated in independent populations by other investigators before wide clinical use since it is unknown whether our score can be applicable for NAFLD patients of other races/ethnics.

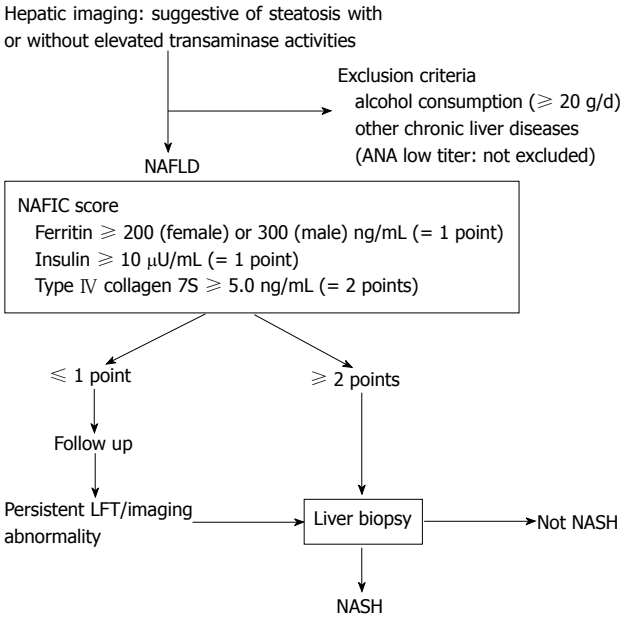


Figure 1 Diagnostic algorithm for nonalcoholic steatohepatitis diagnosis proposed by Japan Study Group of nonalcoholic fatty liver disease. NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis.

CONCLUSION

NAFLD, a manifestation of metabolic syndrome, is a leading cause of CLD worldwide. NASH, the progressive form of NAFLD, can progress to cirrhosis, hepatic failure and hepatocellular carcinoma. It is important to identify patients with NASH. However, there is no simple test to reliably detect NASH apart from liver biopsy. The clinical spectrum of NAFLD warrants continued research to determine its pathogenesis and to improve diagnostic modalities. It is hoped that improved imaging techniques, the discovery of serum biomarkers and the development of clinical algorithms will enable a more accurate diagnosis of NASH without the need for a liver biopsy.

REFERENCES

1 **Ludwig J**, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc* 1980; **55**: 434-438
2 **Schaffner F**, Thaler H. Nonalcoholic fatty liver disease. *Prog Liver Dis* 1986; **8**: 283-298
3 **Sanyal AJ**. AGA technical review on nonalcoholic fatty liver disease. *Gastroenterology* 2002; **123**: 1705-1725
4 **Neuschwander-Tetri BA**, Caldwell SH. Nonalcoholic stea-

tohepatitis: summary of an AASLD Single Topic Conference. *Hepatology* 2003; **37**: 1202-1219
5 **Farrell GC**, Chitturi S, Lau GK, Sollano JD. Guidelines for the assessment and management of non-alcoholic fatty liver disease in the Asia-Pacific region: executive summary. *J Gastroenterol Hepatol* 2007; **22**: 775-777
6 **Ono M**, Saibara T. Clinical features of nonalcoholic steatohepatitis in Japan: Evidence from the literature. *J Gastroenterol* 2006; **41**: 725-732
7 **Hashimoto E**, Tokushige K. Prevalence, gender, ethnic variations, and prognosis of NASH. *J Gastroenterol* 2010; Epub ahead of print
8 **Mofrad P**, Contos MJ, Haque M, Sargeant C, Fisher RA, Luketic VA, Sterling RK, Shiffman ML, Stravitz RT, Sanyal AJ. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. *Hepatology* 2003; **37**: 1286-1292
9 **Uslusoy HS**, Nak SG, Gülten M, Biyikli Z. Non-alcoholic steatohepatitis with normal aminotransferase values. *World J Gastroenterol* 2009; **15**: 1863-1868
10 **Fracanzani AL**, Valenti L, Bugianesi E, Andreoletti M, Colli A, Vanni E, Bertelli C, Fatta E, Bignamini D, Marchesini G, Fargion S. Risk of severe liver disease in nonalcoholic fatty liver disease with normal aminotransferase levels: a role for insulin resistance and diabetes. *Hepatology* 2008; **48**: 792-798
11 **Angulo P**, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology* 1999; **30**: 1356-1362
12 **Angulo P**, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, Enders F, Saksena S, Burt AD, Bida JP, Lindor K, Sanderson SO, Lenzi M, Adams LA, Kench J, Therneau TM, Day CP. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology* 2007; **45**: 846-854
13 **Harrison SA**, Oliver D, Arnold HL, Gogia S, Neuschwander-Tetri BA. Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease. *Gut* 2008; **57**: 1441-1447
14 **Sumida Y**, Yoshikawa T, Okanoue T. Role of hepatic iron in non-alcoholic steatohepatitis. *Hepatol Res* 2009; **39**: 213-222
15 **Saadeh S**, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, Mullen KD, Cooper JN, Sheridan MJ. The utility of radiological imaging in nonalcoholic fatty liver disease. *Gastroenterology* 2002; **123**: 745-750
16 **Dasarathy S**, Dasarathy J, Khiyami A, Joseph R, Lopez R, McCullough AJ. Validity of real time ultrasound in the diagnosis of hepatic steatosis: a prospective study. *J Hepatol* 2009; **51**: 1061-1067
17 **Tobari M**, Hashimoto E, Yatsuji S, Torii N, Shiratori K. Imaging of nonalcoholic steatohepatitis: advantages and pitfalls of ultrasonography and computed tomography. *Intern Med* 2009; **48**: 739-746
18 **Moriyasu F**, Iijima H, Tsuchiya K, Miyata Y, Furusaka A, Miyahara T. Diagnosis of NASH using delayed parenchymal imaging of contrast ultrasound. *Hepatol Res* 2005; **33**: 97-99
19 **Iijima H**, Moriyasu F, Tsuchiya K, Suzuki S, Yoshida M, Shimizu M, Sasaki S, Nishiguchi S, Maeyama S. Decrease in accumulation of ultrasound contrast microbubbles in non-alcoholic steatohepatitis. *Hepatol Res* 2007; **37**: 722-730
20 **Yoneda M**, Suzuki K, Kato S, Fujita K, Nozaki Y, Hosono K, Saito S, Nakajima A. Nonalcoholic fatty liver disease: US-based acoustic radiation force impulse elastography. *Radiology* 2010; **256**: 640-647
21 **Yoneda M**, Yoneda M, Fujita K, Inamori M, Tamano M, Hiriishi H, Nakajima A. Transient elastography in patients with non-alcoholic fatty liver disease (NAFLD). *Gut* 2007; **56**: 1330-1331
22 **Wong VW**, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, Choi PC, Kowo M, Chan AW, Merrouche W, Sung JJ, de Lédinghen V. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. *Hepatology* 2010; **51**: 454-462
23 **Yatsuji S**, Hashimoto E, Kaneda H, Taniai M, Tokushige K, Shiratori K. Diagnosing autoimmune hepatitis in nonalcoholic fatty liver disease: is the International Autoimmune Hepatitis Group scoring system useful? *J Gastroenterol* 2005; **40**: 1130-1138
24 **Niwa H**, Sasaki M, Haratake J, Kasai T, Katayanagi K, Kurumaya H, Masuda S, Minato H, Zen Y, Uchiyama A, Miwa A, Saito K, Sudo Y, Nakanuma Y. Clinicopathological significance of antinuclear antibodies in non-alcoholic steatohepatitis. *Hepatol Res* 2007; **37**: 923-931
25 **Adams LA**, Lindor KD, Angulo P. The prevalence of autoantibodies and autoimmune hepatitis in patients with nonalcoholic Fatty liver disease. *Am J Gastroenterol* 2004; **99**: 1316-1320
26 **Rockey DC**, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. *Hepatology* 2009; **49**: 1017-1044
27 **Tarugi P**, Averna M, Di Leo E, Cefalù AB, Noto D, Magnolo L, Cattin L, Bertolini S, Calandra S. Molecular diagnosis of hypobetalipoproteinemia: an ENID review. *Atherosclerosis* 2007; **195**: e19-e27
28 **Katsuda S**, Kawashiri MA, Inazu A, Tada H, Tsuchida M, Kaneko Y, Nozue T, Nohara A, Okada T, Kobayashi J, Michishita I, Mabuchi H, Yamagishi M. Apolipoprotein B gene mutations and fatty liver in Japanese hypobetalipoproteinemia. *Clin Chim Acta* 2009; **399**: 64-68
29 **Harada N**, Soejima Y, Taketomi A, Yoshizumi T, Uchiyama H, Ikegami T, Saibara T, Nishizaki T, Maehara Y. Recurrent familial hypobetalipoproteinemia-induced nonalcoholic fatty liver disease after living donor liver transplantation. *Liver Transpl* 2009; **15**: 806-809
30 **Powell EE**, Jonsson JR, Clouston AD. Steatosis: co-factor in other liver diseases. *Hepatology* 2005; **42**: 5-13
31 **Powell EE**, Jonsson JR, Clouston AD. Metabolic factors and non-alcoholic fatty liver disease as co-factors in other liver diseases. *Dig Dis* 2010; **28**: 186-191
32 **Sumida Y**, Kanemasa K, Fukumoto K, Yoshida N, Sakai K. Correlation of hepatic steatosis with body mass index, serum ferritin level and hepatic fibrosis in Japanese patients with chronic hepatitis C. *Hepatol Res* 2007; **37**: 263-269
33 **Brunt EM**. What's in a NAme? *Hepatology* 2009; **50**: 663-667
34 **Loria P**, Adinolfi LE, Bellentani S, Bugianesi E, Grieco A, Fargion S, Gasbarrini A, Loguercio C, Lonardo A, Marchesini G, Marra F, Persico M, Prati D, Baroni GS. Practice guidelines for the diagnosis and management of nonalcoholic fatty liver disease. A decalogue from the Italian Association for the Study of the Liver (AISF) Expert Committee. *Dig Liver Dis* 2010; **42**: 272-282
35 **Ratziu V**, Bellentani S, Cortez-Pinto H, Day C, Marchesini G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. *J Hepatol* 2010; **53**: 372-384
36 **Farrell GC**, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* 2006; **43**: S99-S112
37 **Mezey E**, Kolman CJ, Diehl AM, Mitchell MC, Herlong HF. Alcohol and dietary intake in the development of chronic pancreatitis and liver disease in alcoholism. *Am J Clin Nutr* 1988; **48**: 148-151
38 **Thun MJ**, Peto R, Lopez AD, Monaco JH, Henley SJ, Heath CW Jr, Doll R. Alcohol consumption and mortality among middle-aged and elderly U.S. adults. *N Engl J Med* 1997; **337**: 1705-1714
39 **Becker U**, Deis A, Sørensen TI, Grønbaek M, Borch-Johnsen K, Müller CF, Schnohr P, Jensen G. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. *Hepatology* 1996; **23**: 1025-1029
40 **Dunn W**, Xu R, Schwimmer JB. Modest wine drinking and decreased prevalence of suspected nonalcoholic fatty liver disease. *Hepatology* 2008; **47**: 1947-1954
41 **Suzuki A**, Angulo P, St Sauver J, Muto A, Okada T, Lindor K. Light to moderate alcohol consumption is associated with

lower frequency of hypertransaminasemia. *Am J Gastroenterol* 2007; **102**: 1912-1919
42 **Dixon JB**, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. *Gastroenterology* 2001; **121**: 91-100
43 **Okanoue T**, Saibara T, Ono M, Sumida Y, Hashimoto E, Tamura T, Yamada G, Kawada S, Kudo M. JSH Consensus Kobe 2009; Diagnosis and Treatment of NASH. *Kanzo* 2009; **50**: 741-747
44 **Ohtsuka T**, Tsutsumi M, Fukumura A, Tsuchishima M, Takase S. Use of serum carbohydrate-deficient transferrin values to exclude alcoholic hepatitis from non-alcoholic steatohepatitis: a pilot study. *Alcohol Clin Exp Res* 2005; **29**: 236S-239S
45 **Matteoni CA**, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology* 1999; **116**: 1413-1419
46 **Rafiq N**, Bai C, Fang Y, Srishord M, McCullough A, Gramlich T, Younossi ZM. Long-term follow-up of patients with nonalcoholic fatty liver. *Clin Gastroenterol Hepatol* 2009; **7**: 234-238
47 **Kleiner DE**, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, Ferrell LD, Liu YC, Torbenson MS, Unalp-Arida A, Yeh M, McCullough AJ, Sanyal AJ. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005; **41**: 1313-1321
48 **Juluri R**, Vuppalanchi R, Olson J, Unalp A, Van Natta ML, Cummings OW, Tonascia J, Chalasani N. Generalizability of the Nonalcoholic Steatohepatitis Clinical Research Network Histologic Scoring System for Nonalcoholic Fatty Liver Disease. *J Clin Gastroenterol* 2010; Epub ahead of print
49 **Brunt EM**. Nonalcoholic steatohepatitis. *Semin Liver Dis* 2004; **24**: 3-20
50 **Vuppalanchi R**, Unalp A, Van Natta ML, Cummings OW, Sandrasegaran KE, Hameed T, Tonascia J, Chalasani N. Effects of liver biopsy sample length and number of readings on sampling variability in nonalcoholic Fatty liver disease. *Clin Gastroenterol Hepatol* 2009; **7**: 481-486
51 **Goldstein NS**, Hastah F, Galan MV, Gordon SC. Fibrosis heterogeneity in nonalcoholic steatohepatitis and hepatitis C virus needle core biopsy specimens. *Am J Clin Pathol* 2005; **123**: 382-387
52 **Ratziu V**, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, Grimaldi A, Capron F, Poynard T. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology* 2005; **128**: 1898-1906
53 **Janiec DJ**, Jacobson ER, Freeth A, Spaulding L, Blaszyk H. Histologic variation of grade and stage of non-alcoholic fatty liver disease in liver biopsies. *Obes Surg* 2005; **15**: 497-501
54 **Merriman RB**, Ferrell LD, Patti MG, Weston SR, Pabst MS, Aouizerat BE, Bass NM. Correlation of paired liver biopsies in morbidly obese patients with suspected nonalcoholic fatty liver disease. *Hepatology* 2006; **44**: 874-880
55 **Younossi ZM**, Gramlich T, Liu YC, Matteoni C, Petrelli M, Goldblum J, Rybicki L, McCullough AJ. Nonalcoholic fatty liver disease: assessment of variability in pathologic interpretations. *Mod Pathol* 1998; **11**: 560-565
56 **Bravo AA**, Sheth SG, Chopra S. Liver biopsy. *N Engl J Med* 2001; **344**: 495-500
57 **Cadranel JF**, Rufat P, Degos F. Practices of liver biopsy in France: results of a prospective nationwide survey. For the Group of Epidemiology of the French Association for the Study of the Liver (AFEF). *Hepatology* 2000; **32**: 477-481
58 **Sumida Y**, Naito Y, Yoshikawa T. Free Radicals and nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH). *Free Rad Biol Dig Dis Front Gastrointest Res* 2011; in press
59 **Sumida Y**, Nakashima T, Yoh T, Furutani M, Hirohama A, Kakisaka Y, Nakajima Y, Ishikawa H, Mitsuyoshi H, Okanoue T, Kashima K, Nakamura H, Yodoi J. Serum thioredoxin levels as a predictor of steatohepatitis in patients with nonalcoholic fatty liver disease. *J Hepatol* 2003; **38**: 32-38
60 **Hyogo H**, Yamagishi S, Iwamoto K, Arihiro K, Takeuchi M, Sato T, Ochi H, Nonaka M, Nabeshima Y, Inoue M, Ishitobi T, Chayama K, Tazuma S. Elevated levels of serum advanced glycation end products in patients with non-alcoholic steatohepatitis. *J Gastroenterol Hepatol* 2007; **22**: 1112-1119
61 **Kimura Y**, Hyogo H, Yamagishi S, Takeuchi M, Ishitobi T, Nabeshima Y, Arihiro K, Chayama K. Atorvastatin decreases serum levels of advanced glycation endproducts (AGEs) in nonalcoholic steatohepatitis (NASH) patients with dyslipidemia: clinical usefulness of AGEs as a biomarker for the attenuation of NASH. *J Gastroenterol* 2010; **45**: 750-757
62 **Charlton M**, Angulo P, Chalasani N, Merriman R, Viker K, Charatcharoenwitthaya P, Sanderson S, Gawrieh S, Krishnan A, Lindor K. Low circulating levels of dehydroepiandrosterone in histologically advanced nonalcoholic fatty liver disease. *Hepatology* 2008; **47**: 484-492
63 **Sumida Y**, Yonei Y, Kanemasa K, Hara T, Inada Y, Sakai K, Imai S, Hibino S, Yamaguchi K, Mitsuyoshi M, Yasui K, Minami M, Itoh Y, Naito Y, Yoshikawa T, Okanoue T. Lower circulating levels of dehydroepiandrosterone, independent of insulin resistance, is an important determinant of severity of nonalcoholic steatohepatitis in Japanese patients. *Hepatol Res* 2010; **40**: 901-910
64 **Yoneda M**, Nozaki Y, Endo H, Mawatari H, Iida H, Fujita K, Yoneda K, Takahashi H, Kirikoshi H, Inamori M, Kobayashi N, Kubota K, Saito S, Maeyama S, Hotta K, Nakajima A. Serum ferritin is a clinical biomarker in Japanese patients with nonalcoholic steatohepatitis (NASH) independent of HFE gene mutation. *Dig Dis Sci* 2010; **55**: 808-814
65 **Yamauchi N**, Itoh Y, Tanaka Y, Mizokami M, Minami M, Morita A, Toyama T, Yamaguchi K, Fujii H, Okanoue T. Clinical characteristics and prevalence of GB virus C, SEN virus, and HFE gene mutation in Japanese patients with nonalcoholic steatohepatitis. *J Gastroenterol* 2004; **39**: 654-660
66 **Chitturi S**, Weltman M, Farrell GC, McDonald D, Kench J, Liddle C, Samarasinghe D, Lin R, Abeygunasekera S, George J. HFE mutations, hepatic iron, and fibrosis: ethnic-specific association of NASH with C282Y but not with fibrotic severity. *Hepatology* 2002; **36**: 142-149
67 **Jehn M**, Clark JM, Guallar E. Serum ferritin and risk of the metabolic syndrome in U.S. adults. *Diabetes Care* 2004; **27**: 2422-2428
68 **Feldstein AE**, Wieckowska A, Lopez AR, Liu YC, Zein NN, McCullough AJ. Cytokeratin-18 fragment levels as noninvasive biomarkers for nonalcoholic steatohepatitis: a multicenter validation study. *Hepatology* 2009; **50**: 1072-1078
69 **Tsutsui M**, Tanaka N, Kawakubo M, Sheena Y, Horiuchi A, Komatsu M, Nagaya T, Joshita S, Umemura T, Ichijo T, Matsumoto A, Yoshizawa K, Aoyama T, Tanaka E, Sano K. Serum fragmented cytokeratin 18 levels reflect the histologic activity score of nonalcoholic fatty liver disease more accurately than serum alanine aminotransferase levels. *J Clin Gastroenterol* 2010; **44**: 440-447
70 **Kitade M**, Yoshiji H, Noguchi R, Ikenaka Y, Kaji K, Shirai Y, Yamazaki M, Uemura M, Yamao J, Fujimoto M, Mitoro A, Toyohara M, Sawai M, Yoshida M, Morioka C, Tsujimoto T, Kawaratani H, Fukui H. Crosstalk between angiogenesis, cytokeratin-18, and insulin resistance in the progression of non-alcoholic steatohepatitis. *World J Gastroenterol* 2009; **15**: 5193-5199
71 **Kaneda H**, Hashimoto E, Yatsuji S, Tokushige K, Shiratori K. Hyaluronic acid levels can predict severe fibrosis and platelet counts can predict cirrhosis in patients with nonalcoholic fatty liver disease. *J Gastroenterol Hepatol* 2006; **21**: 1459-1465
72 **Yoneda M**, Mawatari H, Fujita K, Yonemitsu K, Kato S, Takahashi H, Kirikoshi H, Inamori M, Nozaki Y, Abe Y, Kubota K, Saito S, Iwasaki T, Terauchi Y, Togo S, Maeyama S, Nakajima A. Type IV collagen 7s domain is an independent clinical marker of the severity of fibrosis in patients with

nonalcoholic steatohepatitis before the cirrhotic stage. *J Gastroenterol* 2007; **42**: 375-381

73 **Shimada M**, Kawahara H, Ozaki K, Fukura M, Yano H, Tsuchishima M, Tsutsumi M, Takase S. Usefulness of a combined evaluation of the serum adiponectin level, HOMA-IR, and serum type IV collagen 7S level to predict the early stage of nonalcoholic steatohepatitis. *Am J Gastroenterol* 2007; **102**: 1931-1938

74 **Guha IN**, Parkes J, Roderick P, Chattopadhyay D, Cross R, Harris S, Kaye P, Burt AD, Ryder SD, Aithal GP, Day CP, Rosenberg WM. Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: Validating the European Liver Fibrosis Panel and exploring simple markers. *Hepatology* 2008; **47**: 455-460

75 **Shah AG**, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2009; **7**: 1104-1112

76 **Fujii H**, Enomoto M, Fukushima W, Tamori A, Sakaguchi H, Kawada N. Applicability of BARD score to Japanese patients with NAFLD. *Gut* 2009; **58**: 1566-1567; author reply 1567

77 **Fujii H**, Enomoto M, Fukushima W, Ohfuji S, Mori M, Kobayashi S, Iwai S, Morikawa H, Tamori A, Sakaguchi H, Ikura Y, Ueda M, Kawada N. Noninvasive laboratory tests proposed for predicting cirrhosis in patients with chronic hepatitis C are also useful in patients with non-alcoholic steatohepatitis. *J Gastroenterol* 2009; **44**: 608-614

78 **Miyaaki H**, Ichikawa T, Nakao K, Yatsuhashi H, Furukawa R, Ohba K, Omagari K, Kusumoto Y, Yanagi K, Inoue O, Kinoshita N, Ishibashi H, Yano M, Eguchi K. Clinicopathological study of nonalcoholic fatty liver disease in Japan: the risk factors for fibrosis. *Liver Int* 2008; **28**: 519-524

79 **Hashimoto E**, Farrell GC. Will non-invasive markers replace liver biopsy for diagnosing and staging fibrosis in non-alcoholic steatohepatitis? *J Gastroenterol Hepatol* 2009; **24**: 501-503

80 **Sumida Y**, Yoneda M, Hyogo H, Yamaguchi K, Ono M, Fujii H, Eguchi Y, Suzuki Y, Imai S, Kanemasa K, Fujita K, Chayama K, Yasui K, Saibara T, Kawada N, Fujimoto K, Kohgo Y, Okanoue T. A simple clinical scoring system using ferritin, fasting insulin, and type IV collagen 7S for predicting steatohepatitis in nonalcoholic fatty liver disease. *J Gastroenterol* 2010; Epub ahead of print

S- Editor Zhang HN **L- Editor** Roemmele A **E- Editor** Liu N

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v2.i10.384

World J Hepatol 2010 October 27; 2(10): 384-386
ISSN 1948-5182 (online)

CASE REPORT

Acute liver failure as a rare initial manifestation of peripheral T-cell lymphoma

Michael L Davis, Nikroo Hashemi

Michael L Davis, Nikroo Hashemi, Department of Gastroenterology and Hepatology, Albert Einstein Medical Center, Philadelphia, Pennsylvania, PA 19141, United States
Author contributions: Davis ML was the fellow and Hashemi N was the attending physician involved with the case; and both authors contributed to the writing, editing, and formatting of the case report.
Correspondence to: Michael L Davis, DO, Department of Gastroenterology and Hepatology, Albert Einstein Medical Center, Philadelphia, Pennsylvania, PA 19141, United States. davisml@einstein.edu
Telephone: +1-215-4568242 Fax: +1-215-4567556
Received: July 19, 2010 Revised: September 4, 2010
Accepted: September 11, 2010
Published online: October 27, 2010

Abstract

Acute liver failure (ALF) is an uncommon disease in the United States, affecting more than 2000 people each year. Of all the various causes, malignant infiltration is one of the least well known and carries with it a high mortality. We describe a case of ALF as the presenting manifestation of peripheral T-cell lymphoma in an elderly woman. By reporting this case, we hope to increase early recognition of this disease process in order to potentially improve treatment outcomes.

Key words: Acute liver failure; Peripheral T-cell lymphoma

Peer reviewers: Smruti Ranjan Mohanty, MD, MS, Assistant Professor of Medicine, Department of Medicine, Section of Gastroenterology & Hepatology, Center for Liver Disease, 5841 S. Maryland Avenue, MC 7120, Chicago, IL 60637-1463, United States; Valentina Medici, MD, PhD, Department of Internal Medicine, University of California Davis, 4150 V Street, Suite 3500, Sacramento, CA 95817, United States; Jordi Muntane, PhD, Unidad de Investigacion, Hospital Universitario Reina Sofía, Av. Menéndez Pidal s/n, Cordoba 14004, Spain

Davis ML, Hashemi N. Acute liver failure as a rare initial manifestation of peripheral T-cell lymphoma. *World J Hepatol* 2010; 2(10): 384-386 Available from: URL: http://www.wjgnet.com/1948-5182/full/v2/i10/384.htm DOI: http://dx.doi.org/10.4254/wjh.v2.i10.384

INTRODUCTION

Acute liver failure (ALF), defined as the presence of encephalopathy and coagulopathy in patients without preexisting liver disease, is an uncommon, although often fatal, condition in the United States[1]. There are over 2000 cases of ALF annually and the overall mortality rate is 80%[2]. Drug-induced (chiefly acetaminophen toxicity) and viral hepatitis comprise the majority of causes of ALF[3]. Other etiologies include: autoimmune hepatitis; acute alcoholic hepatitis; toxins such as *Amanita phalloides;* hepatic circulatory compromise such as shock liver and Budd-Chiari; Wilson's disease; and acute fatty liver of pregnancy.

Among the less common causes of ALF is neoplastic infiltration of the liver. Malignancy can involve the liver either as a primary or secondary site and may cause abnormal liver function tests. Acute liver failure as an initial manifestation of malignant infiltration, however, is quite rare, carries a high mortality, and the diagnosis is often made at autopsy[4-6]. We report a case of peripheral T-cell lymphoma resulting in ALF.

CASE REPORT

A 67-year-old African-American female presented to an outside hospital with a three-day history of progressive confusion, lethargy, and vague abdominal pain. Past medical history was significant only for hypertension, treated with diltiazem. Prior surgeries included cholecystectomy and hysterectomy. She denied any use of alcohol, acetaminophen, or over-the-counter herbs or supplements. She had no risk factors for viral hepatitis, had not travelled recently nor had any sick contacts. On physical examina-

tion she was somnolent but oriented. She was afebrile, but was markedly tachycardic and tachypneic. She had icteric sclerae, a distended, slightly tender abdomen with shifting dullness, and splenomegaly. There was no asterixis. The remainder of the examination was normal. Initial laboratory data were: total bilirubin 4.6 mg/dL, alkaline phosphatase 207 IU/L, aspartate aminotransferase (AST) 418 IU/L, alanine aminotransferase (ALT) 139 IU/L, creatinine 2.15 mg/dL, platelet count 113 × 10^9/L, white blood cell count 11 × 10^9/L, and international normalized ratio (INR) 2.15. She was admitted to the hospital and treated empirically with levofloxacin and intravenous fluids. Further laboratory studies including alcohol and acetaminophen levels, and serologies for hepatitis A, B, C, cytomegalovirus, Epstein-Barr virus, and human immunodeficiency virus were negative. Iron and copper studies and autoimmune markers were all within normal limits. Abdominal ultrasound with dopplers and an abdominal computed tomography (CT) scan without intravenous contrast (not given because of impaired renal function) showed ascites and an enlarged heterogenous spleen with wedge-shaped infarcts; the hepatic parenchyma, vasculature, and biliary ducts were normal. Her clinical and laboratory status deteriorated, and she was transferred to our hospital for liver transplant evaluation one week after her initial presentation. On arrival, she had stage 2-3 encephalopathy and was intubated for airway protection and mechanical ventilation. Laboratory values on admission showed total bilirubin 9.5 mg/dL, alkaline phosphatase 344 IU/L, AST 128 IU/L, ALT 71 IU/L, platelet count 93 × 10^9/L, white blood cell count 35 × 10^9/L (77% neutrophils, 10% bands, 5% lymphocytes), glucose 19, pH 7.18, serum lactate 243 mmol/L and lactate dehydrogenase (LDH) 4660 IU/L. Diagnostic paracentesis revealed an ascitic leukocyte count of 1680 × 10^6/L (84% neutrophils) and serum-ascites albumin gradient (SAAG) 1.2 consistent with spontaneous bacterial peritonitis, and antibiotics were continued. A contrast-enhanced abdominal CT scan showed an enlarged and heterogeneously enhancing liver, with mediastinal, right hilar and chest wall lymphadenopathy, and, splenomegaly with splenic infarcts. A peripheral blood smear showed atypical lymphocytes. A transjugular liver biopsy on hospital d 2 revealed diffuse infiltration of malignant-appearing lymphocytes with immunohistochemistry features supporting a T-cell phenotype. This was consistent with peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). Due to her malignancy, she was therefore not a candidate for liver transplantation. Her clinical status continued to deteriorate, with worsening lactic acidosis, hypoglycemia, and disseminated intravascular coagulation, and she became comatose on hospital d 4. In agreement with her family's wishes, aggressive chemotherapy was withheld and she was managed palliatively. She died 3 d later and 14 d after her initial presentation.

DISCUSSION

Acute liver failure is a rare initial presentation of lymphoma, with less than 40 cases reported in the literature[7]. This phenomenon is twice as likely to occur in men, and the mean age is 48.6 years. It carries an 83% mortality rate, with a mean survival of 10.7 d. Most diagnoses are established by liver biopsy and often occur postmortem. Chemotherapy has only been successful in inducing remission in 3 of 23 cases of non-Hodgkins lymphoma (NHL)-associated ALF[6]. Due to rapid recurrence rates with poor survivability, liver transplantation is contraindicated[8].

Peripheral T-cell lymphomas are malignancies of immunologically mature T-cells that arise in peripheral lymphoid tissues such as lymph nodes, spleen, gastrointestinal tract, and skin. They are a rare and heterogenous class comprising only 5%-10% of NHL in North America and Western Europe[9]. The PTCL-NOS classification represents the largest subgroup, and generally affects people over the age of 60 with a slight male predominance. Due to its aggressive nature, patients often present in advanced stages, with nodal and extranodal spread. In one series of 199 patients diagnosed with PTCL, overall liver involvement occurred in 10%, and, in 9% for the PTCL-NOS subtype[10]. The 5-year survival rate is 20%-30% in most series[9].

This case highlights the importance of considering all the possible causes of ALF once the more common ones have been excluded. A diagnosis of lymphoma should be entertained in any patient presenting with ALF, lactic acidosis, and, hepatomegaly with evidence of an infiltrative process[6]. Unfortunately, given the advanced stage of disease and the wishes of the patient's family, it was decided not to subject our patient to chemotherapy and her condition rapidly deteriorated. Prompt recognition of lymphoma and initiation of chemotherapy, however, may result in better outcomes.

REFERENCES

1 **Polson J**, Lee WM. AASLD position paper: the management of acute liver failure. *Hepatology* 2005; **41**: 1179-1197
2 **Hoofnagle JH**, Carithers RL Jr, Shapiro C, Ascher N. Fulminant hepatic failure: summary of a workshop. *Hepatology* 1995; **21**: 240-252
3 **Ostapowicz G**, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SH, McCashland TM, Shakil AO, Hay JE, Hynan L, Crippin JS, Blei AT, Samuel G, Reisch J, Lee WM. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002; **137**: 947-954
4 **Ghosh P**, Fox IJ, Rader AM, Sorrell MF. Fulminant hepatic failure as the initial manifestation of non-Hodgkins lymphoma. *Am J Gastroenterol* 1995; **90**: 2207-2209
5 **Khashab M**, Tector AJ, Kwo PY. Epidemiology of acute liver failure. *Curr Gastroenterol Rep* 2007; **9**: 66-737
6 **Lettieri CJ**, Berg BW. Clinical features of non-Hodgkins lymphoma presenting with acute liver failure: a report of five cases and review of published experience. *Am J Gastroenterol* 2003; **98**: 1641-1646
7 **Bhat YM**, Krasinskas A, Craig FE, Shaw-Stiffel TA. Acute liver failure as an initial manifestation of an infiltrative hematolymphoid malignancy. *Dig Dis Sci* 2006; **51**: 63-67
8 **Thompson DR**, Faust TW, Stone MJ, Polter DE. Hepatic failure as the presenting manifestation of malignant lymphoma. *Clin Lymphoma* 2001; **2**: 123-128
9 **Vose J**, Armitage J, Weisenburger D. International peripheral

T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol* 2008; **26**: 4124-4130
10 **Savage KJ**, Chhanabhai M, Gascoyne RD, Connors JM. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. *Ann Oncol* 2004; **15**: 1467-1475

S- Editor Zhang HN **L- Editor** Herholdt A **E- Editor** Liu N

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v2.i10.387

World J Hepatol 2010 October 27; 2(10): 387-391
ISSN 1948-5182 (online)

CASE REPORT

Hepatic reactive lymphoid hyperplasia in a patient with primary biliary cirrhosis

Mitsuaki Ishida, Tamio Nakahara, Yousuke Mochizuki, Tomoyuki Tsujikawa, Akira Andoh, Yasuharu Saito, Hiroshi Yamamoto, Fumiyoshi Kojima, Machiko Hotta, Tohru Tani, Yoshihide Fujiyama, Hidetoshi Okabe

Mitsuaki Ishida, Fumiyoshi Kojima, Machiko Hotta, Hidetoshi Okabe, Department of Clinical Laboratory Medicine and Division of Diagnostic Pathology, Shiga University of Medical Science, Otsu, Shiga 520-2192, Japan
Tamio Nakahara, Tomoyuki Tsujikawa, Akira Andoh, Yoshihide Fujiyama, Department of Gastroenterology, Shiga University of Medical Science, Otsu, Shiga 520-2192, Japan
Yousuke Mochizuki, Yasuharu Saito, Division of Endoscopy, Shiga University of Medical Science, Otsu, Shiga 520-2192, Japan
Hiroshi Yamamoto, Tohru Tani, Department of Surgery, Shiga University of Medical Science, Otsu, Shiga 520-2192, Japan
Author contributions: Ishida M interpreted the data; Ishida M and Okabe H wrote the manuscript; and all the authors contributed to analyzing the patient's data.
Correspondence to: Mitsuaki Ishida, MD, PhD, Assistant Professor, Department of Clinical Laboratory Medicine and Division of Diagnostic Pathology, Shiga University of Medical Science, Tsukinowa-cho, Seta, Otsu, Shiga 520-2192, Japan. mitsuaki@belle.shiga-med.ac.jp
Telephone: +81-77-5482603 Fax: +81-77-5482407
Received: May 18, 2010 Revised: August 6, 2010
Accepted: August 13, 2010
Published online: October 27, 2010

Abstract

Reactive lymphoid hyperplasia (RLH) of the liver is an extremely rare lesion characterized by the proliferation of non-neoplastic lymphocytes forming follicles. Hepatic RLH is known to be associated with gastrointestinal carcinoma and autoimmune diseases including primary biliary cirrhosis (PBC). We report a case of hepatic RLH in a patient with PBC and gastric cancer. A 68 year old Japanese woman with a 10 year history of liver enzyme abnormality was admitted. Laboratory testing revealed that her anti-mitochondrial antibody was markedly elevated. Five mo after the diagnosis of PBC, she was found to have gastric cancer. Abdominal computed tomography disclosed a liver nodule in S8, suggesting metastatic gastric carcinoma. Histopathologically, the resected liver lesion comprised of a nodular proliferation of small lymphocytes with lymphoid follicles. This is the first reported case of hepatic RLH in a patient with both PBC and gastric cancer. Pre-operative diagnosis of hepatic RLH by clinical imaging is extremely difficult. Therefore, a needle biopsy could be useful to make a diagnosis of hepatic RLH, especially to differentiate from metastatic gastrointestinal carcinoma.

Key words: Reactive lymphoid hyperplasia; Pseudolymphoma; Liver; Primary biliary cirrhosis; Gastric cancer

Peer reviewers: Hatim Mohamed Yousif Mudawi, Associate Professor of Medicine, Department of Internal Medicine, Faculty of Medicine, University of Khartoum, PO Box 2245, Khartoum, Sudan; Can-Hua Huang, PhD, Oncoproteomics Group, The State Key Laboratory of Biotherapy, Sichuan University, No. 1 Keyuan Rd 4, Gaopeng St, High-Tech Zone, Chengdu 610041, Sichuan Province, China

Ishida M, Nakahara T, Mochizuki Y, Tsujikawa T, Andoh A, Saito Y, Yamamoto H, Kojima F, Hotta M, Tani T, Fujiyama Y, Okabe H. Hepatic reactive lymphoid hyperplasia in a patient with primary biliary cirrhosis. *World J Hepatol* 2010; 2(10): 387-391 Available from: URL: http://www.wjgnet.com/1948-5182/full/v2/i10/387.htm DOI: http://dx.doi.org/10.4254/wjh.v2.i10.387

INTRODUCTION

Reactive lymphoid hyperplasia (RLH) of the liver is an extremely rare lesion characterized by the proliferation of non-neoplastic, polyclonal lymphocytes forming follicles with an active germinal center[1-3]. This lesion has also been reported as pseudolymphoma and nodular lymphoid lesion[4-6]. To the best of our knowledge, only 28 cases of RLH of the liver have been reported in the English literature[7-22].

Herein, we report an additional case of RLH of the liver in a patient with both primary biliary cirrhosis (PBC) and gastric cancer and discuss the clinicopathological features of hepatic RLH and the clinical importance of differential diagnostic consideration of liver lesions in patients with gastrointestinal carcinoma.

CASE REPORT

A 68 year old Japanese female with a ten year history of liver enzyme abnormality was admitted to our hospital for further evaluation of the cause. Laboratory tests disclosed elevated gamma-glutamyl transpeptidase (83 U/L; range 10-47), alkaline phosphatase (568 U/L; range 115-359), leucine aminopeptidase (230 U/L; range 70-180), thymol turbidity (12.2 Kunkel; range 0.0-8.0) and zinc sulfate turbidity (14.1 Kunkel; range 3.0-11.0). Aspartate aminotransferase (28 U/L; range 13-33), alanine aminotransferase (21 U/L; range 6-27), and total bilirubin (0.8 mg/dL; range 0.3-1.2) were within normal ranges. Her serum IgG (1839 mg/dL; range 870-1700) and IgM (306 mg/dL; range 35-220) were slightly elevated. Her anti-mitochondrial antibody (M2) (index 195; range < 7.0) and anti-centromere antibody (index 167; range < 10) were markedly elevated. Both hepatitis B surface antigen and hepatitis C antibody were negative. These laboratory data suggested PBC and a liver biopsy was performed to confirm the diagnosis.

Liver biopsy showed periportal lymphocytic infiltration with bile duct damage (Figure 1). Infiltration of a few eosinophils and neutrophils in the portal area also was observed but granuloma and lymphoid follicle formation were not found. These histopathological findings were consistent with PBC. In addition, no histopathological evidence suggesting liver cirrhosis was seen.

Five mo after the liver biopsy, an upper gastrointestinal endoscopic examination revealed a depressed lesion with spontaneous hemorrhage and irregular margins in the pylorus region of minor curvature (Figure 2). Biopsy of the depressed gastric lesion disclosed signet ring cell carcinoma. Abdominal contrast-enhanced computed tomography (CT) showed a small nodule measuring 2cm with early enhancement in S8 of the liver (Figure 3), suggesting metastatic gastric carcinoma. Serum tumor markers were within normal ranges (CA19-9 17 U/mL; range < 37, carcinoembryonic antigen 2.6 ng/mL; range < 5, alpha-fetoprotein 2.6 ng/mL; range < 20, protein induced by vitamin K absence Ⅱ (PIVKA Ⅱ) 14 mAU/mL; range < 40).

Distal gastrectomy and resection of the liver nodule were performed.

Histopathologically, the gastric carcinoma was a signet ring cell carcinoma invading into the deep submucosa (pT1) (Figure 4A). No lymphatic or vascular invasion was detected by immunostaining of D2-40 or elastica van Gieson stain and no lymph node metastasis was seen (pN0).

Histopathological study of the resected liver lesion disclosed a relatively well-circumscribed nodular proliferation of mature-appearing small lymphocytes with lymphoid follicles (Figure 4B). The lymphoid follicles varied in size (Figure 4B, C). The germinal centers comprised a mixture of small and large lymphoid cells and scattered tingible body macrophages accompanied by a well-developed mantle zone (Figure 4C). Interfollicular areas were mostly composed of small mature-appearing lymphocytes and a small number of infiltrating plasma cells and histiocytes were also found (Figure 4C). No granuloma formation or multinucleated giant cells were observed. Mature-appearing lymphocytes were aggregated in the portal areas around the nodule. No lymphoepithelial lesion of bile

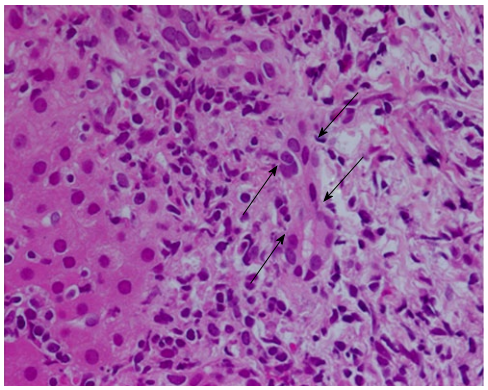


Figure 1 Histopathological findings of the liver biopsy. Periportal lymphocytic infiltration with bile duct damage (arrows: damaged bile duct; hematoxylin and eosin stain, × 400).

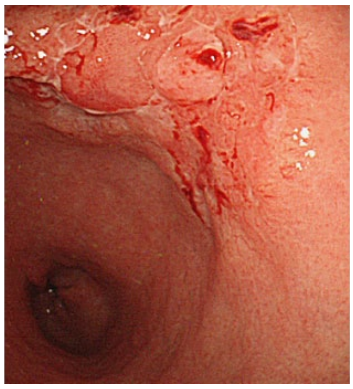


Figure 2 Endoscopic picture of the stomach. The depressed lesion with spontaneous hemorrhage and irregular margins.

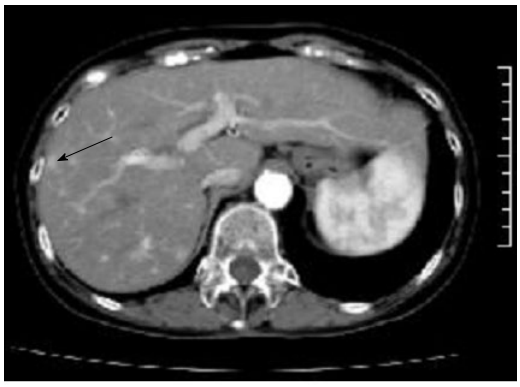


Figure 3 Contrast-enhanced abdominal computed tomography. A well-circumscribed nodule showing early arterial enhancement in S8 (arrow).

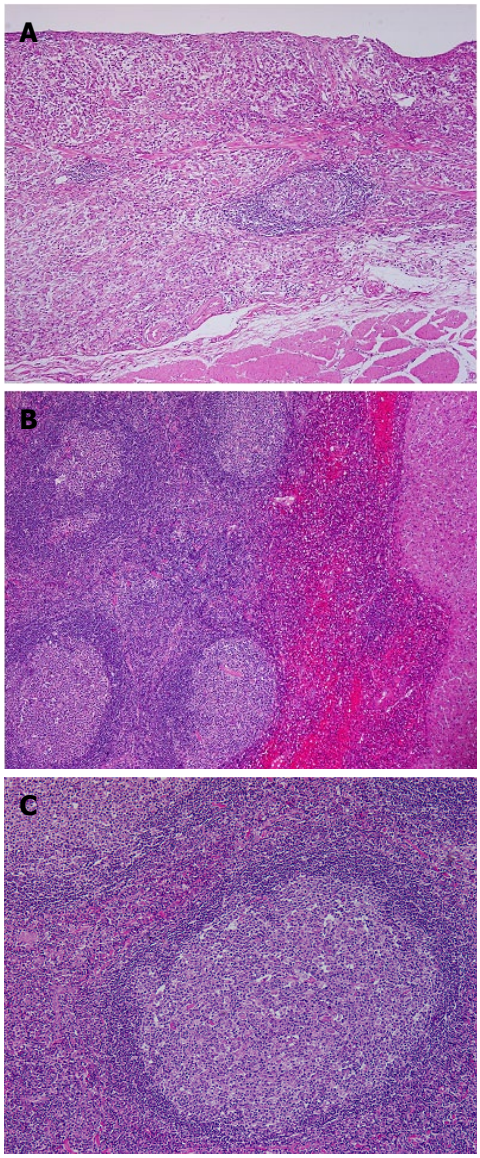


Figure 4 Histopathological findings of the gastric carcinoma and liver nodule. A: Signet ring cell carcinoma of the stomach invading into the deep submucosa (hematoxylin and eosin stain, × 40); B: A relatively well-circumscribed nodular proliferation of lymphocytes with lymphoid follicles in the liver (right: liver parenchyma, hematoxylin and eosin stain, × 40); C: Mantle zone and germinal center are sharply demarcated and a mixture of small and large lymphocytes and scattered tingible body macrophages is observed in the germinal center (hematoxylin and eosin stain, × 40).

duct was observed. In addition, no metastatic gastric carcinoma was disclosed.

Immunohistochemical studies showed that CD3-positive T lymphocytes and CD20/79a-positive B lymphocytes were regularly distributed in the same manner as in the lymph node (Figure 5). Bcl-2 was negative for lymphoid follicles. *In situ* hybridization of immunoglobulin light chains revealed intermixed kappa chain- and lambda chain-positive plasma cells.

Although polymerase chain reaction analysis of the immunoglobulin heavy chain gene was not performed, these histopathological and immunohistochemical findings were consistent with RLH of the liver.

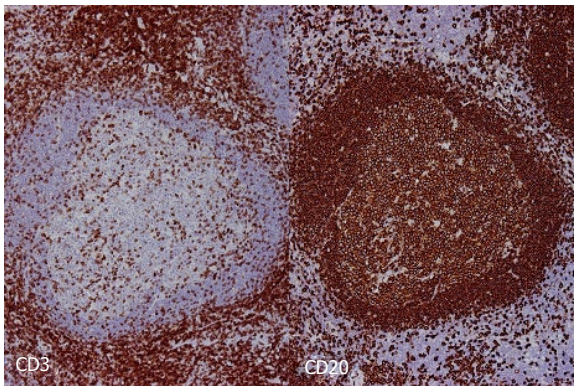


Figure 5 Immunohistochemical findings of the liver nodule. CD3-positive T lymphocytes (left) and CD20-positive B lymphocytes (right) are regularly distributed (× 40).

Post-operatively, no obvious recurrence of the liver no dule was detected during the 3 mo medical follow-up.

DISCUSSION

RLH can occur in various organs such as the gastrointestinal tract[23], lung[24] and skin[25]. RLH of the liver is extremely rare and most previous reports have been one case report, although recently Zen *et al*[5] reported the clinicopathological features of 5 cases of hepatic RLH. We review the clinicopathological features of the 28 cases of hepatic RLH reported previously in the English literature as well as the present case, as shown in Table 1. There is a very high female predominance (4 males/25 females). The youngest patient, reported by Snover *et al*[7], was a 15 year old female who had primary immunodeficiency syndrome. Except for that case, all patients were adult (range 36-85 years; average 59). Six of 29 cases (21%) had multiple lesions (five cases had two and one case had three lesions). The diameter of the lesions ranged from 0.4 to 5.5 cm; however, most were less than 2 cm.

Interestingly, five cases (17%) of hepatic RLH, including the present case, had a history of PBC (Table 1). In addition, six patients (21%) had extrahepatic autoimmune diseases such as Sjögren syndrome[16], Hashimoto thyroiditis[1], Takayasu arteritis[5], antiphospholipid syndrome[5] and CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia) syndrome[6]; one patient had both PBC and CREST syndrome[6] and one patient had both PBC and chronic thyroiditis[5] (Table 1). The relatively high prevalence of autoimmune disease (approximately 30%) in patients with hepatic RLH suggests that systemic and/or local immunological abnormalities could be associated with the development of hepatic RLH, as suggested by earlier reports[14,16].

Moreover, the prevalence of gastrointestinal carcinoma in patients with hepatic RLH is also relatively high; seven patients (24%) with hepatic RLH had gastrointestinal carcinomas (Table 1). Three patients, including the present case, had gastric cancer and three patients had colon

Table 1 Clinicopathological features of reactive lymphoid hyperplasia of the liver

Case No.	Age	Sex	Number of lesions	Size (cm)	Associated disease	Ref.
1	15	F	1	NA	Primary immunodeficiency syndrome	[7]
2	85	F	2	1.4, 1.8	Gastric cancer	[8]
3	59	F	1	0.9	Diabetes mellitus	[9]
4	42	F	2	1.5, 1.4	Hepatitis B, IFN-alpha therapy	[10]
5	66	F	1	1.5	Diabetes mellitus, non-alcoholic steatohepatitis	[11]
6	67	M	1	2.0	Abnormal liver function	[12]
7	72	F	1	1.7	Hepatitis C, gastric cancer	[13]
8	52	F	1	0.4	Primary biliary cirrhosis	[6]
9	56	M	1	1.5	Primary biliary cirrhosis, CREST syndrome	[6]
10	56	F	1	0.7	Diverticulitis	[6]
11	47	F	1	1.7	Chronic thyroiditis	[14]
12	69	F	1	1.7	Renal cell carcinoma	[15]
13	49	F	1	2.0	Sjogren syndrome	[16]
14	77	F	1	1.5	Colon cancer	[2]
15	64	F	1	0.9	Colon cancer	[2]
16	72	F	1	1.3		[17]
17	36	F	1	1.8	Foca nodular hyperplasia and hemangioma of the liver	[18]
18	75	F	1	1.4	Gastric and colon cancers, liver metastasis (colon cancer)	[3]
19	63	F	1	1.6	Gastric ulcer	[19]
20	53	F	3	1.3, 1.1, 0.8	Autoimmune thyroiditis	[1]
21	67	F	1	1.2	Hypertension	[20]
22	46	F	1	1.0	Renal cell carcinoma	[21]
23	63	F	2	1.3, 0.4	Primary biliary cirrhosis, primary aldosteronism	[4]
24	63	F	2	0.9, 0.5	Primary biliary cirrhosis, chronic thyroiditis, adrenocortical adenoma	[5]
25	40	M	1	2.0	Hepatitis B	[5]
26	81	M	1	5.5	Cholecystolithiasis	[5]
27	64	F	2	3.5, 1.0	Takayasu arteritis, antiphospholipid syndrome	[5]
28	44	F	1	1.5	Colon cancer	[22]
Present case	68	F	1	2.0	Primary biliary cirrhosis, gastric cancer	

NA: not available; Ref: references.

cancer. Sato *et al*[3] reported a case of hepatic RLH in a patient with double carcinomas of the stomach and colon and a metastatic liver lesion from the latter. This is the first case report of hepatic RLH in a patient with both PBC and gastric cancer. Zen *et al*[5] speculated that the antigen from the gastrointestinal tract through the portal vein participates in the pathogenesis of hepatic RLH.

Although the precise mechanism of development of hepatic RLH remains unclear, these results suggest that autoimmune and/or immune reaction to the gastrointestinal malignancies may be involved in its development. In the present case, the patient had both PBC and gastric cancer simultaneously and either one or both may have been associated with the development of hepatic RLH.

Histopathologically, it is important to distinguish RLH from low-grade malignant lymphoma, especially marginal zone B cell lymphoma[5]. In the present case, the resected liver lesion disclosed nodular proliferation of mature-appearing small lymphocytes forming lymphoid follicles with a germinal center and neither lymphoepithelial lesion nor atypia of infiltrative lymphocytes were observed. The diagnosis of hepatic RLH was not difficult in the present case. However, making a diagnosis of hepatic RLH by needle biopsy can be challenging[5]. It has been reported that lymphoepithelial lesions and cellular atypia of infiltrating lymphocytes are important to provide a differential diagnosis[5]. In addition, all of the marginal zone lymphoma in the liver showed a dense portal lymphocytic infiltrate and a nodular proliferative pattern is rare in marginal zone lymphoma[26]. These findings suggest that cellular atypia and infiltrative pattern could be helpful in making a differential diagnosis.

Pre-operative diagnosis of hepatic RLH by clinical imaging is extremely difficult because hepatic RLH has features similar to hepatocellular carcinoma on various imaging modalities; namely a hypoechoic mass on ultrasound, low density on CT with or without enhancement and low intensity on T1-weighted imaging and high intensity on T2-weighted imaging with magnetic reso nance imaging[1,2]. In addition, these diagnostic imaging findings cannot rule out the possibility of metastatic carcinoma in patients with gastrointestinal carcinoma[2]. In the present case, the liver lesion was diagnosed pre-operatively as metastasis of gastric carcinoma. Therefore, a pre-operative liver biopsy could be useful for dis tinguishing hepatic RLH from metastatic gastrointestinal carcinoma and hepatocellular carcinoma, although differential diagnosis from low-grade malignant lymphoma could be challenging.

In summary, we report the first case of hepatic RLH in a patient with both PBC and gastric carcinoma. Pre-operative diagnosis of hepatic RLH by clinical imaging is extremely difficult. Therefore, a needle biopsy could be useful for making a diagnosis of hepatic RLH, especially in differentiating from metastatic gastrointestinal carcinoma and hepatocellular carcinoma, although distinguishing

hepatic RLH from low-grade malignant lymphoma could be challenging.

REFERENCES

1 **Machida T**, Takahashi T, Itoh T, Hirayama M, Morita T, Horita S. Reactive lymphoid hyperplasia of the liver: a case report and review of literature. *World J Gastroenterol* 2007; **13**: 5403-5407
2 **Takahashi H**, Sawai H, Matsuo Y, Funahashi H, Satoh M, Okada Y, Inagaki H, Takeyama H, Manabe T. Reactive lymphoid hyperplasia of the liver in a patient with colon cancer: report of two cases. *BMC Gastroenterol* 2006; **6**: 25
3 **Sato K**, Ueda Y, Yokoi M, Hayashi K, Kosaka T, Katsuda S. Reactive lymphoid hyperplasia of the liver in a patient with multiple carcinomas: a case report and brief review. *J Clin Pathol* 2006; **59**: 990-992
4 **Okada T**, Mibayashi H, Hasatani K, Hayashi Y, Tsuji S, Kaneko Y, Yoshimitsu M, Tani T, Zen Y, Yamagishi M. Pseudolymphoma of the liver associated with primary biliary cirrhosis: a case report and review of literature. *World J Gastroenterol* 2009; **15**: 4587-4592
5 **Zen Y**, Fujii T, Nakanuma Y. Hepatic pseudolymphoma: a clinicopathological study of five cases and review of the literature. *Mod Pathol* 2010; **23**: 244-250
6 **Sharifi S**, Murphy M, Loda M, Pinkus GS, Khettry U. Nodular lymphoid lesion of the liver: an immune-mediated disorder mimicking low-grade malignant lymphoma. *Am J Surg Pathol* 1999; **23**: 302-308
7 **Snover DC**, Filipovich AH, Dehner LP, Krivit W. 'Pseudolymphoma'. A case associated with primary immunodeficiency disease and polyglandular failure syndrome. *Arch Pathol Lab Med* 1981; **105**: 46-49
8 **Grouls V**. Pseudolymphoma (inflammatory pseudotumor) of the liver. *Zentralbl Allg Pathol* 1987; **133**: 565-568
9 **Isobe H**, Sakamoto S, Sakai H, Masumoto A, Sonoda T, Adachi E, Nawata H. Reactive lymphoid hyperplasia of the liver. *J Clin Gastroenterol* 1993; **16**: 240-244
10 **Ohtsu T**, Sasaki Y, Tanizaki H, Kawano N, Ryu M, Satake M, Hasebe T, Mukai K, Fujikura M, Tamai M. Development of pseudolymphoma of liver following interferon-alpha therapy for chronic hepatitis B. *Intern Med* 1994; **33**: 18-22
11 **Katayanagi K**, Terada T, Nakanuma Y, Ueno T. A case of pseudolymphoma of the liver. *Pathol Int* 1994; **44**: 704-711
12 **Tanizawa T**, Eishi Y, Kamiyama R, Nakahara M, Abo Y, Sumita T, Kawano N. Reactive lymphoid hyperplasia of the liver characterized by an angiofollicular pattern mimicking Castleman's disease. *Pathol Int* 1996; **46**: 782-786
13 **Kim SR**, Hayashi Y, Kang KB, Soe CG, Kim JH, Yang MK, Itoh H. A case of pseudolymphoma of the liver with chronic hepatitis C. *J Hepatol* 1997; **26**: 209-214
14 **Nagano K**, Fukuda Y, Nakano I, Katano Y, Toyoda H, Nonami T, Nagasaka T, Hayakawa T. Reactive lymphoid hyperplasia of liver coexisting with chronic thyroiditis: radiographical characteristics of the disorder. *J Gastroenterol Hepatol* 1999; **14**: 163-167
15 **Pantanowitz L**, Saldinger PF, Kadin ME. Pathologic quiz case: Hepatic mass in a patient with renal cell carcinoma. *Arch Pathol Lab Med* 2001; **125**: 577-578
16 **Okubo H**, Maekawa H, Ogawa K, Wada R, Sekigawa I, Iida N, Maekawa T, Hashimoto H, Sato N. Pseudolymphoma of the liver associated with Sjögren's syndrome. *Scand J Rheumatol* 2001; **30**: 117-119
17 **Maehara N**, Chijiiwa K, Makino I, Ohuchida J, Kai M, Kondo K, Moriguchi S, Marutsuka K, Asada Y. Segmentectomy for reactive lymphoid hyperplasia of the liver: Report of a case. *Surg Today* 2006; **36**: 1019-1023
18 **Willenbrock K**, Kriener S, Oeschger S, Hansmann ML. Nodular lymphoid lesion of the liver with simultaneous focal nodular hyperplasia and hemangioma: discrimination from primary hepatic MALT-type non-Hodgkin's lymphoma. *Virchows Arch* 2006; **448**: 223-237
19 **Ota H**, Isoda N, Sunada F, Kita H, Higashisawa T, Ono K, Sato S, Ido K, Sugano K. A case of hepatic pseudolymphoma observed without surgical intervention. *Hepatol Res* 2006; **35**: 296-301
20 **Matsumoto N**, Ogawa M, Kawabata M, Tohne R, Hiroi Y, Furuta T, Yamamoto T, Gotoh I, Ishiwata H, Ono Y, Arakawa Y, Kinukawa N. Pseudolymphoma of the liver: Sonographic findings and review of the literature. *J Clin Ultrasound* 2007; **35**: 284-288
21 **Park HS**, Jang KY, Kim YK, Cho BH, Moon WS. Histiocyte-rich reactive lymphoid hyperplasia of the liver: unusual morphologic features. *J Korean Med Sci* 2008; **23**: 156-160
22 **Lin E**. Reactive lymphoid hyperplasia of the liver identified by FDG PET. *Clin Nucl Med* 2008; **33**: 419-420
23 **Kojima M**, Itoh H, Motegi A, Sakata N, Masawa N. Localized lymphoid hyperplasia of the rectum resembling polypoid mucosa-associated lymphoid tissue lymphoma: a report of three cases. *Pathol Res Pract* 2005; **201**: 757-761
24 **Abbondanzo SL**, Rush W, Bijwaard KE, Koss MN. Nodular lymphoid hyperplasia of the lung: a clinicopathologic study of 14 cases. *Am J Surg Pathol* 2000; **24**: 587-597
25 **Medeiros LJ**, Picker LJ, Abel EA, Hu CH, Hoppe RT, Warnke RA, Wood GS. Cutaneous lymphoid hyperplasia. Immunologic characteristics and assessment of criteria recently proposed as diagnostic of malignant lymphoma. *J Am Acad Dermatol* 1989; **21**: 929-942
26 **Loddenkemper C**, Longerich T, Hummel M, Ernestus K, Anagnostopoulos I, Dienes HP, Schirmacher P, Stein H. Frequency and diagnostic patterns of lymphomas in liver biopsies with respect to the WHO classification. *Virchows Arch* 2007; **450**: 493-502

S- Editor Zhang HN **L- Editor** Roemmele A **E- Editor** Liu N

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v2.i10.392

World J Hepatol 2010 October 27; 2(10): 392-394
ISSN 1948-5182 (online)

CASE REPORT

Acute liver failure caused by concurrent autoimmune hepatitis and hepatitis B in a 16-year old girl

Małgorzata Pawłowska, Waldemar Halota

Małgorzata Pawłowska, Waldemar Halota, Department of Infectious Diseases and Hepatology, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz 85-030, Poland
Author contributions: Pawlowska M and Halota W contributed equally to this work; and Both of them were responsible for data analysis and paper writing.
Correspondence to: Małgorzata Pawłowska, MD, PhD, Professor, Department of Infectious Diseases and Hepatology, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz 85-030, Poland. mpawlowska@cm.umk.pl
Telephone: +48-52-3255605 Fax: +48-52-3457195
Received: June 24, 2010 Revised: September 3, 2010
Accepted: September 10, 2010
Published online: October 27, 2010

Abstract

A 16 year-old girl was admitted to hospital because of fatigue and somnolence, nausea, epistaxis and jaundice. Physical examination revealed jaundice, an enlarged liver and tenderness of upper right abdomen. Laboratory tests revealed an increased level of acute liver failure, bilirubin, bile acids, GGTP and a decreased prothrombin ratio, with elevated gamma-globulin and IgG levels, and the presence of anti-mitochondrial M2 antibodies and HBV infection markers. The patient was diagnosed with liver failure resulting from chronic hepatitis B with an autoimmune component. The treatment consisted of steroids, azathioprine, vitamin K, low-protein diet and lactulose enemas. After undergoing a molecular test (HBV DNA 3.23 × 10^5 IU/mL and mutations I 204 and I 80), the treatment was modified by adding entecavir. After one month the patient was discharged in good clinical condition, with the recommendation of continued entecavir, prednisone and azathioprine. In subsequent months, no clinical deterioration or abnormal biochemical liver function test results were found, despite the discontinuation of immunosuppressive therapy after 10 mo. The patient continues entecavir therapy.

Key words: Acute liver failure; Chronic hepatitis B; Autoimmune hepatitis; Adolescent

Peer reviewers: K Rajeshwari, Professor, Department of Pediatrics, Maulana Azad Medical College, Bahadur Shah Zafar Marg, New Delhi 110002, India; Felix Dias Carvalho, Faculty of Pharmacy, Professor, Toxicology Department, University of Porto, Rua Anibal Cunha, Porto 4099-033, Portugal; Shahinul Alam, MBBS, FCPS, MD, Department of Hepatology, BSM Medical University, Dhanmobdi R/A, Dhaka 1000, Bangladesh

Pawłowska M, Halota W. Acute liver failure caused by concurrent autoimmune hepatitis and hepatitis B in a 16-year old girl. *World J Hepatol* 2010; 2(10): 392-394 Available from: URL: http://www.wjgnet.com/1948-5182/full/v2/i10/392.htm DOI: http://dx.doi.org/10.4254/wjh.v2.i10.392

INTRODUCTION

In Poland, the number of persons with chronic HBV infection is estimated at 400000, and HBV or HCV infection is the most frequent cause of chronic hepatitis in children.

The natural history of HBV infection in children is different from that of adults. It commonly takes the form of asymptomatic chronic infection, most often diagnosed incidentally or as a result of epidemiological investigation. In children, the disease usually remains asymptomatic for many years, and children acquiring the infection in the early period of life are at high risk of clinical sequelae, which may present in adulthood. The infection in an early period of life is often associated with a high HBV DNA replication rate, presence of HBe antigen in serum with normal alanine aminotransferase (ALT) levels, and minor abnormalities of liver histology[1].

Autoimmune hepatitis (AIH) is the leading cause of chronic liver disease in the regions where HLA B8 DR3

haplotype is common, and the prevalence of chronic viral hepatitis is low. Based on the presence of certain types of antibodies, AIH is divided into 2 main types: type 1 with antinuclear antibodies (ANA) and/or anti-smooth muscle antibodies (ASMA), and type 2 with anti liver-kidney microsome antibodies (anti-LKM). Acute liver failure is more frequent in patients with type 2 AIH, and particularly young women or adolescent girls[2]. In autoimmune liver diseases, in addition to the most common overlap syndromes of AIH/primary biliary cirrhosis (AIH/PBC) and AIH/primary primary sclerosing cholangitis (AIH/PSC), an AIH/viral hepatitis (AIH/VH) variant is distinguished. When establishing the diagnosis of this syndrome it is important to differentiate between AIH with positive viral infection markers, and chronic viral hepatitis with positive autoimmune markers. In the majority of the latter cases, viral components are predominant, and the disease is successfully treated with antiviral drugs. Much less often, the autoimmune components are predominant, and viral infection markers coexist (AIH/VH); such cases respond well to steroid treatment[3].

Gergiadou *et al* have reported occult HBV infections with concurrent autoimmune liver disease. The occult HBV infections did not promote progression of AIH. Moreover, no patient had a reactivation of HBV infection during immunosuppressive treatment[4]. To date, no HBV infection with concurrent AIH has been reported in children.

We report a case of acute liver failure in the course of chronic hepatitis B with a component of autoimmune hepatitis.

CASE REPORT

A 16 year-old girl (initials P.P.; medical record No.689/2008) was admitted to hospital because of fatigue and somnolence, which increased over a week, nausea and loose stools lasting 3 d, epistaxis and jaundice.

Her past medical history included 2 hospitalizations in infancy, and surgery for a left forearm fracture at the age of 12. One year later she received the hepatitis B vaccine without prior HBs antigen testing.

Her general condition at admission was rated as quite good. Physical examination revealed jaundiced skin and sclerae, enlarged liver and tenderness of upper right abdomen. During hospitalization the patient complained of fatigue, skin pruritus, abdominal pain and headache. She also had epistaxis, somnolence and loss of appetite.

Laboratory test results revealed elevated aminotransferases (ALT: 1115 U/L, AST: 647 U/L), as well as elevated bilirubin, with predominant conjugate bilirubin, (respectively 9.41 mg/dL and 6.43 mg/dL), bile acids (216 mol/L), GGTP (60 U/L) and decreased prothrombin ratio (56%). Serum protein electrophoresis revealed elevated gamma-globulin (3.60 g/dL) and decreased albumin (3.82 g/dL) levels, and immunoglobulin tests revealed elevated IgG (34.7g/L) levels and the presence of anti-mitochondrial M2 (AMA M2) antibodies.

Serologic tests revealed the presence of HBV infection markers: HBsAg, HBeAg, total and IgM anti-HBc, and an anti-HBs level of 326 IU/L. The HAV, HCV, EBV, CMV, and Toxoplasma infections were excluded, as well as Wilson's disease and alpha-1 antitripsin deficiency.

The patient was diagnosed with liver failure resulting from chronic hepatitis B with autoimmune component. The treatment consisted of steroids, azathioprine, vitamin K, low-protein diet and lactulose enemas.

In the first days of hospitalization, despite the above therapy, increasing levels of liver damage markers were observed. On d 7, after receiving molecular test results confirming high HBV replication (HBV DNA 3.23 × 10^5 IU/mL) and presence of HBV polymerase gene mutations in codons I 204 and I 80, the treatment was modified by adding 1 mg entecavir daily. From the second week of therapy, a gradual clinical improvement was observed, with concomitant decrease of aminotransferase and bilirubin levels and increase of prothrombin ratio. On d 30, the HBV viral load had decreased to 6.05 × 10^3, ALT levels had decreased to 48 U/L, prothrombin ratio had increased to 90% and gamma-globulin levels had decreased to 1.91g/dL. AMA M2 antibodies; HBe antigens were still detectable in serum.

The patient was discharged in good clinical condition with the recommendation of continued entecavir, prednisone and azathioprine, and systematic follow up in the Hepatology Clinic. After another month of treatment ALT levels normalized, and, after another three months the HBV viral load became negative. Steroid and azathioprine doses were reduced, with continued antiviral treatment.

Six mo from the onset of the disease, a liver biopsy was performed. The liver histology revealed altered architecture of the liver, with trabecular thickening, loss of continuity of the basal lamina at ¼ of its circumference due to inflammatory infiltrate, expanded portal spaces, features of balloon degeneration of hepatocytes and multiple focal necrosis of lobules with periportal necrosis. Histological diagnosis of chronic hepatitis B was established, with Grade 1 inflammatory activity, and Grade 2 fibrosis according to modified Scheuer's scale.

In subsequent months, no clinical deterioration nor abnormal biochemical liver function test results were found, despite the discontinuation, after 10 mo, of immunosuppressive therapy. The patient continues entecavir therapy. The serologic tests still reveal the presence of HBsAg and HBeAg, with undetectable HBV replication, normal serum ALT and protein levels and negative AMA M2 antibodies.

DISCUSSION

We have described a patient with liver failure in the course of chronic hepatitis B with autoimmune component. To our knowledge, it is the first report of a pediatric patient with exacerbation of hepatitis B and concurrent AIH.

By definition, the diagnosis of autoimmune hepatitis is based on typical criteria and the exclusion of other causes

of liver disease, including viral infection. In children, the use of the generally accepted AIH classification is virtually impossible in view of the criteria employed, such as alcohol intake, or the presence of viral infections (EBV, CMV, HHV-6), which may initiate autoimmune processes or autoantibody production[5,6]. Using this classification we would not have been able to diagnose AIH in our patient because of the presence of HBV infection and AMA M2 antibodies. ANA and ASMA are known to be present in 20% to 40% patients with HBV infection, but there are no reports of the positive AMA, particularly AMA M2 typical for PBC, in patients with HBV infection[7]. The diagnosis of PBC in our case is excluded by the histology of the liver and the minor increase of GGTP levels.

Viral infections may induce autoimmune processes. Tabak *et al* described AIH in the course of prolonged viral hepatitis A Michalska *et al* reported the emergence of autoimmune processes within 5 to 18 years from the diagnosis of chronic hepatitis B in 5 HBe-negative patients[8,9].

In our patient, the dominant role of HBV infection as a cause of both autoimmune processes and liver fai lure, was confirmed not only histologically, but also clinically - by rapid improvement after the HBV-specific antiviral treatment with entacavir was started, as well as by sustained normalization of liver function tests and immu nological markers, despite the discontinuation of immunosuppressive therapy. The reason for the use of this specific nucleoside analogue was the patient's clinical characteristics - features of liver failure, presence of mutations associated with resistance to lamivudine and presence of autoimmune processes. It was also justified by a high genetic barrier of entecavir. Entecavir combined with immunosuppressive agents proved effective in the treatment of liver failure in the course of HBV infection with concurrent autoimmune process.

It is difficult to speculate whether HBV infection in our patient took place before the administration of the hepatitis B vaccine, or whether the vaccine failed to protect the patient from infection. Our patient was found to be infected with a mutant HBV strain. In the literature there are few reports on the effectiveness of the hepatits B vaccine against strains other than wild-type HBV[10,11].

It would also be very interesting to learn whether infection with a virus with altered genome nucleotide sequences predisposes the emergence of autoimmune abnormalities, including autoimmune processes. In the era of the increasing problem of HBV mutations, this might be of much importance for both the clinical aspects and the epidemiology of HBV infection.

REFERENCES

1 **Pawłowska M**, Halota W. Treatment of chronic hepatitis B In children. *Exp Clin Hepatol* 2008; **4**: 38-40
2 **Mieli-Vergani G**, Vergani D. Autoimmune paediatric liver disease. *World J Gastroenterol* 2008; **14**: 3360-3367
3 **Czaja AJ**. Frequency and nature of the variant syndromes of autoimmune liver disease. *Hepatology* 1998; **28**: 360-367
4 **Georgiadou SP**, Zachou K., Liaskos CH, Gabeta S, Rigopoulou EI, Dalekos GN. Occult hepatitis B virus infection in patients with autoimmune liver diseases. *Liver Int* 2009; 434-442
5 **Alvarez F**, Berg PA, Bianchi FB. International Autoimmune hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol* 1999; **31**: 929-938
6 **Fujisawa T**, Sogo T, Komatsu H. Autoimmune hepatitis in childhood. *Hepatol Res* 2007; **37**: 496-500
7 **Gregorio GV**, Choudhuri K, Ma Y. Mimicry between the hepatitis B Virus DNA polymerase and the Antigenic Targets of Nuclear and Smooth Muscle Antibodies In Chronic hepatitis B virus infection. *J Immunol* 1999; **162**: 1802-1810
8 **Michalska Z**, Stalke P, Witczak-Malinowska K, Lakomy EA, Sikorska K, Radowska D, Stolarczyk J, Trocha H. Autoimmune reactions in HBV and HCV. *Med Sci Monit* 2001; **7** Suppl 1: 175-180
9 **Tabak F**, Ozdemir F, Tabak O, Erer B, Tahan V, Ozaras R. Autoimmune hepatitis induced by the prolonged hepatitis A virus infection. *Ann Hepatol* 2008; **7**: 177-179
10 **Clements CJ**, Coghlan B, Creati M, Locarnini S, Tedder RS, Torresi J. Global control of hepatitis B virus: does treatment-induced antigenic change affect immunization? *Bull World Health Organ* 2010; **88**: 66-73
11 **Locarini S**. Transmission of antiviral drug resistant hepatitis B virus: Implications for public health and patient management. *J Gastroenterol Hepatol* 2010; **25**: 649-656

S- Editor Zhang HN **L- Editor** Herholdt A **E- Editor** Liu N

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
www.wjgnet.com

World J Hepatol 2010 October 27; 2(10): I
ISSN 1948-5182 (online)

Acknowledgments to reviewers of *World Journal of Hepatology*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Hepatology*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

Shahinul Alam, MBBS, FCPS, MD, Department of Hepatology, BSM Medical University, Dhanmobdi R/A, Dhaka 1000, Bangladesh

Felix Dias Carvalho, Faculty of Pharmacy, Professor, Toxicology Department, University of Porto, Rua Anibal Cunha, Porto 4099-033, Portugal

Stephen Lam Chan, MD, Department of Clinical Oncology, The Chinese University of Hong Kong, Prince of Wales Hospital, 30-32 Ngan Street, Shatin, New Territories, Hong Kong, China

Norberto Carlos Chavez-Tapia, MD, PhD, Departments of Biomedical Research, Gastroenterology & Liver Unit, Medica Sur Clinic & Foundation, Puente de Piedra 150, Col. Toriello Guerra, Tlalpan 14050, Mexico City, Mexico

Can-Hua Huang, PhD, Oncoproteomics Group, The State Key Laboratory of Biotherapy, Sichuan University, No. 1 Keyuan Rd 4, Gaopeng St, High-Tech Zone, Chengdu 610041, Sichuan Province, China

Wan Yee Joseph Lau, MD, Professor, Clinical Sciences Building, Prince of Wales Hospital, Shatin, New Territories, Hong Kong, China

Amedeo Lonardo, MD, Internal Medicine, Endocrinology, Metabolism and Geriatrics, University of Modena and Reggio Emilia, Modena 41100, Italy

Valentina Medici, MD, PhD, Department of Internal Medicine, University of California Davis, 4150 V Street, Suite 3500, Sacramento, CA 95817, United States

Smruti Ranjan Mohanty, MD, MS, Assistant Professor of Medicine, Department of Medicine, Section of Gastroenterology & Hepatology, Center for Liver Disease, 5841 S. Maryland Avenue, MC 7120, Chicago, IL 60637-1463, United States

Zenichi Morise, MD, PhD, Department of Surgery, Fujita Health University School of Medicine, 1-98 Dengakugakubo Kutsukakecho, Toyoake, AICHI 470-1192, Japan

Hatim Mohamed Yousif Mudawi, Associate Professor of Medicine, Department of Internal Medicine, Faculty of Medicine, University of Khartoum, PO Box 2245, Khartoum, Sudan

Jordi Muntane, PhD, Unidad de Investigacion, Hospital Universitario Reina Sofía, Av. Menéndez Pidal s/n, Cordoba 14004, Spain

Andrea Nicolini, Professor, Department of Internal Medicine, University of Pisa, via Roma 67, Pisa 56126, Italy

Derek Anthony O'Reilly, PhD, FRCS, Department of Surgery, North Manchester General Hospital, Delaunays Road, Manchester, M8 5RB, United Kingdom

Eileen M O'Reilly, Associate Member, MSKCC, Associate Professor, Cornell University Medical Center, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 324, New York, NY 10065, United States

K Rajeshwari, Professor, Department of Pediatrics, Maulana Azad Medical College, Bahadur Shah Zafar Marg, New Delhi 110002, India

Xun-Di Xu, MD, PhD, Department of Gastroenterological Surgery, Xiangya 2nd Hospital, Central South University, Renmin Zhong Road 139, Changsha 410011, Hunan Province, China

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
www.wjgnet.com

World J Hepatol 2010 October 27; 2(10): I
ISSN 1948-5182 (online)

Meetings

Events Calendar 2010

January 25-26
Tamilnadu, India
International Conference on Medical Negligence and Litigation in Medical Practice

January 25-29
Waikoloa, HI, United States
Selected Topics in Internal Medicine

January 26-27
Dubai, United Arab Emirates
2nd Middle East Gastroenterology Conference

March 04-06
Bethesda, MD, United States
8th International Symposium on Targeted Anticancer Therapies

March 05-07
Peshawar, Pakistan
26th Pakistan Society of Gastroenterology & Endoscopy Meeting

March 12-14
Bhubaneswar, India
18th Annual Meeting of Indian National Association for Study of the Liver

March 25-28
Beijing, China
The 20th Conference of the Asian Pacific Association for the Study of the Liver

March 27-28
San Diego, California, United States
25th Annual New Treatments in Chronic Liver Disease

April 07-09
Dubai, United Arab Emirates
The 6th Emirates Gastroenterology and Hepatology Conference, EGHC 2010

April 14-18
Vienna, Austria
The International Liver Congress™ 2010

May 01-05
New Orleans, LA, United States
Digestive Disease Week Annual Meeting

May 06-08
Munich, Germany
The Power of Programming: International Conference on Developmental Origins of Health and Disease

June 04-06
Chicago, IL, United States
American Society of Clinical Oncologists Annual Meeting

June 16-19
Hong Kong, China
ILTS: International Liver Transplantation Society ILTS Annual International Congress

September 10-12
Montreal, Canada
International Liver Association's Fourth Annual Conference

September 12-15
Boston, MA, United States
ICAAC: Interscience Conference on Antimicrobial Agents and Chemotherapy Annual Meeting

September 16-18
Prague, Czech Republic
Prague Hepatology Meeting 2010

September 23-26
Prague, Czech Republic
The 1st World Congress on Controversies in Gastroenterology & Liver Diseases

October 15-20
San Antonio, TX, United States
ACG 2010: American College of Gastroenterology Annual Scienitfic Meeting

October 23-27
Barcelona, Spain
18th United European Gastroenterology Week

October 29-November 02
Boston, Massachusetts, United States
The Liver Meeting® 2010--AASLD's 61st Annual Meeting

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
www.wjgnet.com

World J Hepatol 2010 October 27; 2(10): I-V
ISSN 1948-5182 (online)

Instructions to authors

GENERAL INFORMATION

World Journal of Hepatology (*World J Hepatol, WJH*, online ISSN 1948-5182, DOI: 10.4254), is a monthly, openaccess, peer-reviewed journal supported by an editorial board of 572 experts in hepatology from 45 countries..

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results.

Maximization of personal benefits

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJH* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJH* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJH* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

Aims and scope

The major task of *WJH* is to rapidly report the most recent results in basic and clinical research on hepatology, specifically including autoimmune, cholestatic and biliary disease, cirrhosis and its complications, liver biology/pathobiology, liver failure, growth , liver failure/cirrhosis/portal hypertension, liver fibrosis, hepatitis B and C virus infection, hepatocellular carcinoma, biliary tract disease, transplantation, genetics, epidemiology, microbiology and inflammatory disorders, molecular and cell biology, nutrition, geriatric hepatology, pediatric hepatology, steatohepatitis and metabolic liver disease, diagnosis and screening, endoscopy, imaging and advanced technology.

Columns

The columns in the issues of *WJH* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Article: To report innovative and original findings in hepatology; (9) Brief Article: To briefly report the novel and innovative findings in hepatology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJH*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of hepatology; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on basic research and clinical practice in hepatology.

Name of journal

World Journal of Hepatology

CSSN

ISSN 1948-5182 (online)

Indexed and Abstracted in

PubMed Central

Published by

Baishideng Publishing Group Co., Limited

SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

Biostatistical editing

Statisital review is performed after peer review. We invite an expert in Biomedical Statistics from to evaluate the statistical

method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement

In the interests of transparency and to help reviewers assess any potential bias, *WJH* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interestsin relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent

Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights

When reporting the results from experiments, authors should follow the highest standards and the trial should comform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Bo ok Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of Baishideng Publishing Group Co., Limited, and may not be reproduced by any means, in whole or in part, without the written permission of both the authors and the publisher. We reserve the right to copy-edit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the International Committee of Medical Journal Editors to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-accessible registry at its outset. The only register now available, to our knowledge, is http://www. clinicaltrials.gov sponsored by the United States National Library of Medicine and we encourage all potential contributors to register with it. However, in the case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

Authors should retain one copy of the text, tables, photographs and illustrations because rejected manuscripts will not be returned to the author(s) and the editors will not be responsible for loss or damage to photographs and illustrations sustained during mailing.

Online submissions

Manuscripts should be submitted through the Online Submission System at: http://www.wjgnet.com/1948-5182 office. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/1948-5182/g_info_20100316080002.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to wjh@wjgnet.com, or by telephone: +86-10-59080038. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

All contributions should be written in English. All articles must be submitted using word-processing software. All submissions must be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Style should conform to our house format. Required information for each of the manuscript sections is as follows:

Title page

Title: Title should be less than 12 words.

Running title: A short running title of less than 6 words should be provided.

Authorship: Authorship credit should be in accordance with the standard proposed by International Committee of Medical Journal Editors, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Institution: Author names should be given first, then the complete name of institution, city, province and postcode. For example, Xu-Chen Zhang, Li-Xin Mei, Department of Pathology, Chengde Medical College, Chengde 067000, Hebei Province, China. One author may be represented from two institutions, for example, George Sgourakis, Department of General, Visceral, and Transplantation Surgery, Essen 45122, Germany; George Sgourakis, 2nd Surgical Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

Supportive foundations: The complete name and number of supportive foundations should be provided, e.g., Supported by National Natural Science Foundation of China, No. 30224801

Correspondence to: Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. All the letters in the email should be in lower case. A space interval should be inserted between country name and email address. For example, Montgomery Bissell, MD, Professor of Medicine, Chief, Liver Center, Gastroenterology Division, University of California, Box 0538, San Francisco, CA 94143, United States. montgomery.bissell@ucsf.edu

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g., Telephone: +86-10-85381892 Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision for acceptance is made only when at least two experts recommend an article for publication. Reviewers for accepted manuscripts are acknowledged in each manuscript, and reviewers of articles which were not accepted will be acknowledged at the end of each issue. To ensure the quality of the articles published in *WJH*, reviewers of accepted manuscripts will be announced by publishing the name, title/position and institution of the reviewer in the footnote accompanying the printed article. For example, reviewers: Professor Jing-Yuan Fang, Shanghai Institute of Digestive Disease, Shanghai, Affiliated Renji Hospital, Medical Faculty, Shanghai Jiaotong University, Shanghai, China; Professor Xin-Wei Han, Department of Radiology, The First Affiliated Hospital, Zhengzhou University, Zhengzhou, Henan Province, China; and Professor Anren Kuang, Department of Nuclear Medicine, Huaxi Hospital, Sichuan University, Chengdu, Sichuan Province, China.

Abstract

There are unstructured abstracts (no more than 256 words) and structured abstracts (no more than 480). The specific requirements for structured abstracts are as follows:

An informative, structured abstracts of no more than 480 words should accompany each manuscript. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim as the form of "To investigate/study/…; MATERIALS AND METHODS (no more than 140 words); RESULTS (no more than 294 words): You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$; CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Text

For articles of these sections, original articles, rapid communication and case reports, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/1948-5182/g_info_list.htm.

Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A:...; B:...; C:...; D:...; E:...; F:...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

Tables

Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

Coding system

The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation

content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn' s disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

PMID and DOI

Pleased provide PubMed citation numbers to the reference list, e.g. PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

Style for journal references

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

Style for book references

Authors: the name of the first author should be typed in bold-faced letters. The surname of all authors should be typed with the initial letter capitalized, followed by their abbreviated middle and first initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR) Book title. Publication number. Publication place: Publication press, Year: start page and end page.

Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/1948-5182/g_info_20100107115140.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and

on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

Examples for paper writing

Editorial: http://www.wjgnet.com/1948-5182/g_info_20100316080004.htm

Frontier: http://www.wjgnet.com/1948-5182/g_info_20100315103153.htm

Topic highlight: http://www.wjgnet.com/1948-5182/g_info_20100316080006.htm

Observation: http://www.wjgnet.com/1948-5182/g_info_20100107112630.htm

Guidelines for basic research: http://www.wjgnet.com/1948-5182/g_info_20100315103748.htm

Guidelines for clinical practice: http://www.wjgnet.com/1948-5182/g_info_20100315103829.htm

Review: http://www.wjgnet.com/1948-5182/g_info_20100107112834.htm

Original articles: http://www.wjgnet.com/1948-5182/g_info_20100107113351.htm

Brief articles: http://www.wjgnet.com/1948-5182/g_info_20100315104523.htm

Case report: http://www.wjgnet.com/1948-5182/g_info_20100107113649.htm

Letters to the editor: http://www.wjgnet.com/1948-5182/_info_20100107114003.htm

Book reviews: http://www.wjgnet.com/1948-5182/g_info_20100315105017.htm

Guidelines: http://www.wjgnet.com/1948-5182/g_info_20100315105107.htm

SUBMISSION OF THE REVISED MANUSCRIPTS AFTER ACCEPTED

Please revise your article according to the revision policies of *WJH*. The revised version including manuscript and high-resolution image figures (if any) should be copied on a floppy or compact disk. The author should send the revised manuscript, along with printed high-resolution color or black and white photos, copyright transfer letter, and responses to the reviewers by courier (such as EMS/DHL).

Editorial Office

World Journal of Hepatology
Editorial Department: Room 903, Building D,
Ocean International Center,
No. 62 Dongsihuan Zhonglu,
Chaoyang District, Beijing 100025, China
Telephone: +86-10-59080038
Fax: +86-10-85381893
E-mail: wjh@wjgnet.com
http://www.wjgnet.com

Language evaluation

The language of a manuscript will be graded before it is sent for revision. (1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing needed; and (4) Grade D: rejected. Revised articles should reach Grade A or B.

Copyright assignment form

Please download a Copyright assignment form from http://www.wjgnet.com/1948-5182/g_info_20100107114726.htm.

Responses to reviewers

Please revise your article according to the comments/suggestions provided by the reviewers. The format for responses to the reviewers' comments can be found at: http://www.wjgnet.com/1948-5182/g_info_20100107114601.htm.

Proof of financial support

For paper supported by a foundation, authors should provide a copy of the document and serial number of the foundation.

Links to documents related to the manuscript

WJH will be initiating a platform to promote dynamic interactions between the editors, peer reviewers, readers and authors. After a manuscript is published online, links to the PDF version of the submitted manuscript, the peer-reviewers' report and the revised manuscript will be put on-line. Readers can make comments on the peer reviewer's report, authors' responses to peer reviewers, and the revised manuscript. We hope that authors will benefit from this feedback and be able to revise the manuscript accordingly in a timely manner.

Science news releases

Authors of accepted manuscripts are suggested to write a science news item to promote their articles. The news will be released rapidly at EurekAlert/AAAS (http://www.eurekalert.org). The title for news items should be less than 90 characters; the summary should be less than 75 words; and main body less than 500 words. Science news items should be lawful, ethical, and strictly based on your original content with an attractive title and interesting pictures.

Publication fee

Authors of accepted articles must pay a publication fee. EDITORIAL, TOPIC HIGHLIGHTS, BOOK REVIEWS and LETTERS TO THE EDITOR are published free of charge.