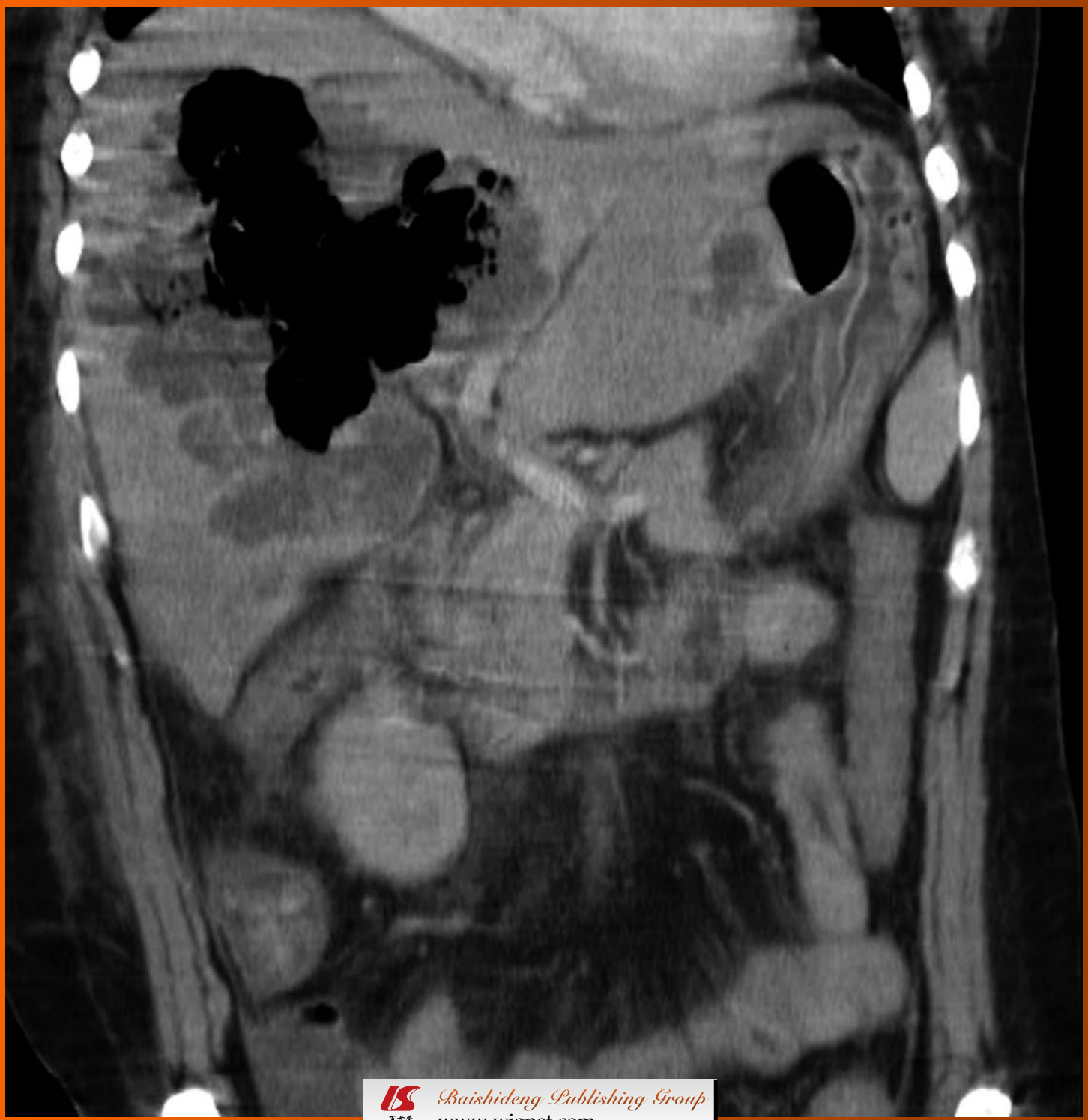
ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2012 August 27; 4(8): 237-255



Baishideng Publishing Group
www.wjgnet.com

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 573 members, representing a team of worldwide experts in hepatology. They are from 46 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), Denmark (1), 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).

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*

World Journal of Hepatology

Contents

Monthly Volume 4 Number 8 August 27, 2012

Contents

World Journal of Hepatology
Volume 4 Number 8 August 27, 2012

AIM AND SCOPE

World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a monthly, open-access, peer-reviewed journal supported by an editorial board of 573 experts in hepatology from 46 countries.

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

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
Monthly

PUBLISHER
Baishideng Publishing Group Co., Limited
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai,
Hong Kong, China
Fax: +852-31158812
Telephone: +852-58042046
E-mail: bpg@baishideng.com
http://www.wjgnet.com

PUBLICATION DATE
August 27, 2012

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
doi:10.4254/wjh.v4.i8.237

World J Hepatol 2012 August 27; 4(8): 237-241
ISSN 1948-5182 (online)

EDITORIAL

Treatment strategy for colorectal cancer with resectable synchronous liver metastases: Is any evidence-based strategy possible?

Luca Viganò

Luca Viganò, Department of HPB and Digestive Surgery, Ospedale Mauriziano "Umberto I", Torino 10128, Italy
Author contributions: Viganò L Solely contributed to this paper.
Correspondence to: Luca Viganò, MD, Department of HBP and Digestive Surgery, Ospedale Mauriziano "Umberto I", Largo Turati 62, Torino 10128, Italy. lvigano@ymail.com
Telephone: +39-11-5082590 Fax: +39-11-5082592
Received: April 22, 2012 Revised: August 10, 2012
Accepted: August 23, 2012
Published online: August 27, 2012

Abstract

Fifteen percent to twenty-five percent of patients affected by colorectal cancer presents with liver metastases at diagnosis. In resectable cases, surgery is the only potentially curative treatment and achieves survival rates up to 50% at 5 years. Management is complex, as colorectal resection, liver resection, chemotherapy, and, in locally advanced mid/low rectal tumors, radiotherapy have to be integrated. Modern medical practice usually relies on evidence-based protocols. Levels of evidence for synchronous metastases are poor: published studies include few recent prospective series and several retrospective analyses collecting a limited number of patients across long periods of time. Data are difficult to be generalized and are mainly representative of single centre's experience, biased by local recruitment, indications and surgical technique. In this context, surgeons have to renounce to "evidence-based medicine" and to adopt a sort of "experience-based medicine". Anyway, some suggestions are possible. Simultaneous colorectal and liver resection can be safely performed whenever minor hepatectomies are planned, while a case-by-case evaluation is mandatory in case of more complex procedures. Neoadjuvant chemotherapy is preferentially scheduled for patients with advanced metastatic tumors to assess disease biology and to control lesions. It can be safely performed with primary tumor *in situ*, even planning simultaneous resection at its end. Locally advanced mid/low rectal tumor represents a further indication to neoadjuvant therapies, even if treatment's schedule is not yet standardized. In summary, several issues have to be solved, but every single HPB centre should define its proper strategy to optimize patient's selection, disease control and safety and completeness of surgery.

Key words: Synchronous liver metastases; Colorectal liver metastases; Liver surgery; Simultaneous colorectal and liver resection; Preoperative chemotherapy; Upfront chemotherapy; Neoadjuvant chemo-radiotherapy; Locally advanced rectal cancer; Survival

Peer reviewers: Yo-ichi Yamashita, MD, PhD, Department of Surgery, Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital, Senda-machi 1-9-6, Naka-ku, Hiroshim 730-8619, Japan; Volker Fendrich, MD, Department of Surgery, Philipps-University, Marburg 35039, Germany

Viganò L. Treatment strategy for colorectal cancer with resectable synchronous liver metastases: Is any evidence-based strategy possible? *World J Hepatol* 2012; 4(8): 237-241 Available from: URL: http://www.wjgnet.com/1948-5182/full/v4/i8/237.htm DOI: http://dx.doi.org/10.4254/wjh.v4.i8.237

INTRODUCTION

Fifteen to 25% of patients affected by colorectal cancer presents with liver metastases at diagnosis[1,2]. In resectable cases, surgery is the only potentially curative treatment[3-5] and achieves survival rates up to 50% at 5 years[6,7]. Management is complex, as colorectal resection, liver resection, chemotherapy, and, in locally advanced mid/low rectal tumors, radiotherapy have to be integrated.

Modern medical practice usually relies on evidence-based protocols. Levels of evidence for synchronous metastases are poor: published studies include few recent prospective series and several retrospective analyses collecting a limited number of patients across long periods of time. Data are difficult to be generalized and are mainly representative of single centre's experience, biased by local recruitment, indications and surgical technique. In this context, surgeons have to renounce to "evidence-based medicine" and to adopt a sort of "experience-based medicine"[8].

SIMULTANEOUS COLORECTAL AND LIVER RESECTION: IS IT BENEFICIAL OR DETRIMENTAL?

The timing of colorectal and liver surgery (simultaneous *vs* staged) has been debated since the 1980s. Theoretically, simultaneous resections have an increased risk of both anastomotic leak (splanchnic congestion after liver surgery) and liver failure (septic complications due to the combination of "clean" and "contaminated" procedures)[9-11]. These fears had not been confirmed in recent studies that reported similar outcomes after simultaneous and delayed resections[7,12-19]. Anyway, the debate is still open: favorable data concerned "easy" resections. What about simultaneous major hepatectomies?

The largest available series are summarized in Table 1. In 2007, Capussotti *et al*[20] compared 31 simultaneous major liver resections with 48 staged ones. Mortality rates were similar in the two groups; considering the two hospitalizations of delayed resections, morbidity and hospital stay resulted even lower in the simultaneous group (33% *vs* 56% and 14 d *vs* 20 d, respectively). These data have been recently confirmed by a few other series[15,21]. On the contrary, a US multicentre database reported increased mortality and morbidity rates after simultaneous major hepatectomy (8% *vs* 1% and 44% *vs* 27%, respectively)[18]. How to conciliate these discrepancies? It is an unsolved question. Simultaneous resections can be neither recommended nor contraindicated. Obviously, patient's selection is mandatory to achieve good outcomes. Particular attention should be paid to the elderly patients, who experienced the worst outcomes[22,23]. Thus, in the absence of evidence and avoiding dogmatic positions, every single centre may adopt its proper preferred policy.

PREOPERATIVE CHEMOTHERAPY: SYSTEMATIC *VS* SELECTIVE INDICATIONS

Even if surgery is the optimal treatment of patients with colorectal metastases, some resectable patients do not benefit from immediate resection because of rapidly progressive disease or of microscopic neoplastic foci that lead to early recurrence[24,25]. How to select good candidates? A time test, i.e., an interval of time before resection, has been proposed. At present, neoadjuvant chemotherapy is the standard time test, allowing tumor biology evaluation, disease control and microscopic foci sterilization[26].

Despite strong theoretical advantages, practical evidences are weak. In 2008 a RCT compared outcomes of patients undergoing surgery with or without perioperative chemotherapy: treated patients had higher disease-free survival rates, but effects of pre- and postoperative chemotherapy resulted indistinguishable[26]. Two retrospective series, specifically focused on synchronous metastases, failed to demonstrate any survival advantage in patients receiving systematic neoadjuvant treatments[27,28].

Selective indications might be adopted. The presence of more than three lymph node metastases has been proposed, but this criterion is difficult to be preoperatively ascertained[29]. In 2007 a study by the author's centre demonstrated that preoperative treatment was useful for selecting patients with T4 primary tumors or with more than three metastases[30]. Additional indications can be proposed on a logical basis: ill-located lesions (disease shrinkage enables easier R0 resection) and presence of extra-hepatic disease. Further studies are needed to codify these indications.

IS SIMULTANEOUS COLORECTAL AND LIVER SURGERY SYNONYMOUS FOR IMMEDIATE RESECTION?

If neoadjuvant chemotherapy is scheduled, the commonest strategy is colorectal surgery followed by chemotherapy, and then liver surgery[31,32]. In the past, the anticipated risk of intestinal occlusion while on therapy precluded any possibility to plan simultaneous resection at the end of treatment. Some authors even criticized simultaneous surgery because of the impossibility to perform any patient's selection[24,25,33].

At present, simultaneous resection is no more synonymous for immediate resection at diagnosis. Recent series demonstrated that up-front chemotherapy with primary tumor *in situ* could be safely administered in unresectable patients[34-40]. The occlusion risk is low, mainly thanks to the effectiveness of modern chemotherapies on primary tumor (Table 2). Furthermore, endoscopic metallic stents may treat symptomatic patients before chemotherapy or even while on treatment[41].

Similar outcomes can be expected in resectable patients. However, only few published simultaneous resections have been preceded by chemotherapy. In the author's centre this strategy has been regularly applied since many years. A retrospective analysis of 40 consecutive patients scheduled for up-front chemotherapy followed by simultaneous colorectal and hepatic resection between 2005 and 2009 demonstrated that a disease control was achieved in 97.5% of patients, an obstructive syndrome occurred in only 7.5%, a simultaneous resection was

Table 1 Outcome of simultaneous *vs* staged major liver resections

Author	Year	Patients		Mortality			Morbidity		
		SimRes	Del	SimRes (%)	Del (%)	*P* value	SimRes (%)	Del (%)	*P* value
Martin *et al*[15][1]	2003	45	76	4	4	NS	60	70	0.03
Thelen *et al*[22]	2007	15	142	26.7	1.4	0.0007	NR	NR	
Reddy *et al*[18][2]	2007	36	291	8.3	1.4	0.03	44.4	26.8	0.04
Capussotti *et al*[20][1]	2007	31	48	3.2	0	NS	32.6	56.3	0.04
de Santibañes *et al*[23]	2010	42	-	4.7	-	-	37.2	-	-
Luo *et al*[21]	2010	44	133	NR	NR		56.8	57.1	NS

[1]In delayed liver resections, morbidity of both hospitalizations (colorectal surgery and liver surgery) is considered; [2]Simultaneous colorectal and major liver resection *vs* other isolated liver resections. SimRes: Simultaneous colorectal and major liver resection; Del: Delayed major liver resection; NR: Data not reported; NS: Not significant.

Table 2 Outcome of "Up-front chemotherapy" strategy: risk of emergency surgery while on treatment *n* (%)

Author	Year	Patients	Resectable at diagnosis	Oxaliplatin- or Irinotecan-based chemotherapy (%)	Emergency surgery
Benoist *et al*[37]	2005	27	No	67	4 (14.8)
Muratore *et al*[38]	2007	35	No	100	1 (2.8)
Poultsides *et al*[39]	2009	233	No	100	16 (7)
Karoui *et al*[40]	2011	123	No	90	15 (12.1)
Viganò/Capussotti[1]	2012	40	Yes	100	3 (7.5)

[1]Unpublished data.

feasible in 95%, and the 3-year survival rate was 75% (unpublished data). These promising results need to be validated by larger prospective studies.

METASTATIC LOCALLY ADVANCED MID/LOW RECTAL CANCER: WHAT ABOUT RADIOTHERAPY?

Neoadjuvant chemo-radiotherapy is the gold standard for patients with non-metastatic locally advanced (T3-4 and/or N+) mid/low rectal cancer to reduce local relapse[42,43]. The inclusion of radiotherapy in the treatment of metastatic patients presents some problems, as high-dose systemic chemotherapy regimens are needed to control hepatic disease, but chemotherapy doses must be reduced in association with radiations in order to limit toxicity[44]. Currently, there is no consensus about the optimal treatment.

In 2006, Mentha *et al*[45] proposed a "reverse" strategy, i.e., a two-stage surgery with liver resection as the first procedure. It easily enables the inclusion of radiations before rectal surgery (the second surgical step). Encouraging results were reported (4-year survival rate of 56%). In 2001 a cooperative study between the author's centre and the Cherqui one (Henri Mondor Hospital, Créteil, France) collected 36 patients[46]. The adopted strategy was up-front neoadjuvant chemotherapy and/or chemo-radiotherapy, according to liver disease extension, followed by simultaneous rectal and liver resection. Five-year survival rate was 59% and no pelvic recurrence occurred among patients who correctly completed the treatment strategy. Further, systemic chemotherapy achieved primary tumor downsizing in most cases, questioning the real need for radiations.

Stronger evidences are needed to consider any possible strategy as the optimal one.

CONCLUSION

No evidence-based conclusions can be drawn, but some suggestions are possible. Simultaneous colorectal and liver resection can be safely performed whenever minor hepatectomies are planned, while a case-by-case evaluation is mandatory in case of more complex procedures. Neoadjuvant chemotherapy is preferentially scheduled for patients with advanced metastatic tumors to assess disease biology and to control lesions. It can be safely performed with primary tumor *in situ*, even planning simultaneous resection at its end. Locally advanced mid/low rectal tumor represents a further indication to neoadjuvant therapies, even if treatment's schedule is not yet standardized.

Several issues have to be solved, but every single HPB centre should define its proper strategy to optimize patient's selection, disease control and safety and completeness of surgery.

REFERENCES

1 **Manfredi S**, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg* 2006; **244**: 254-259

2 **Simmonds PC**, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from

colorectal cancer: a systematic review of published studies. *Br J Cancer* 2006; **94**: 982-999
3 **Minagawa M**, Makuuchi M, Torzilli G, Takayama T, Kawasaki S, Kosuge T, Yamamoto J, Imamura H. Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. *Ann Surg* 2000; **231**: 487-499
4 **Tomlinson JS**, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, Kemeny N, Brennan MF, Blumgart LH, D'Angelica M. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007; **25**: 4575-4580
5 **Viganò L**, Ferrero A, Lo Tesoriere R, Capussotti L. Liver surgery for colorectal metastases: results after 10 years of follow-up. Long-term survivors, late recurrences, and prognostic role of morbidity. *Ann Surg Oncol* 2008; **15**: 2458-2464
6 **Viganò L**, Russolillo N, Ferrero A, Langella S, Sperti E, Capussotti L. Evolution of long-term outcome of liver resection for colorectal metastases: analysis of actual 5-year survival rates over two decades. *Ann Surg Oncol* 2012; **19**: 2035-2044
7 **Brouquet A**, Mortenson MM, Vauthey JN, Rodriguez-Bigas MA, Overman MJ, Chang GJ, Kopetz S, Garrett C, Curley SA, Abdalla EK. Surgical strategies for synchronous colorectal liver metastases in 156 consecutive patients: classic, combined or reverse strategy? *J Am Coll Surg* 2010; **210**: 934-941
8 **Viganò L**, Langella S, Ferrero A, Russolillo N, Sperti E, Capussotti L. Colorectal cancer with synchronous resectable liver metastases: monocentric management in HPB referral center improves survival outcomes. *Ann Surg Oncol* 2012; In press
9 **Vogt P**, Raab R, Ringe B, Pichlmayr R. Resection of synchronous liver metastases from colorectal cancer. *World J Surg* 1991; **15**: 62-67
10 **Nordlinger B**, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, Jaeck D. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Française de Chirurgie. *Cancer* 1996; **77**: 1254-1262
11 **Belghiti J**. [Synchronous and resectable hepatic metastases of colorectal cancer: should there be a minimum delay before hepatic resection?]. *Ann Chir* 1990; **44**: 427-429; discussion 429-432
12 **Lyass S**, Zamir G, Matot I, Goitein D, Eid A, Jurim O. Combined colon and hepatic resection for synchronous colorectal liver metastases. *J Surg Oncol* 2001; **78**: 17-21
13 **de Santibañes E**, Lassalle FB, McCormack L, Pekolj J, Quintana GO, Vaccaro C, Benati M. Simultaneous colorectal and hepatic resections for colorectal cancer: postoperative and longterm outcomes. *J Am Coll Surg* 2002; **195**: 196-202
14 **Weber JC**, Bachellier P, Oussoultzoglou E, Jaeck D. Simultaneous resection of colorectal primary tumour and synchronous liver metastases. *Br J Surg* 2003; **90**: 956-962
15 **Martin R**, Paty P, Fong Y, Grace A, Cohen A, DeMatteo R, Jarnagin W, Blumgart L. Simultaneous liver and colorectal resections are safe for synchronous colorectal liver metastasis. *J Am Coll Surg* 2003; **197**: 233-241; discussion 241-242
16 **Tanaka K**, Shimada H, Matsuo K, Nagano Y, Endo I, Sekido H, Togo S. Outcome after simultaneous colorectal and hepatic resection for colorectal cancer with synchronous metastases. *Surgery* 2004; **136**: 650-659
17 **Chua HK**, Sondenaa K, Tsiotos GG, Larson DR, Wolff BG, Nagorney DM. Concurrent vs. staged colectomy and hepatectomy for primary colorectal cancer with synchronous hepatic metastases. *Dis Colon Rectum* 2004; **47**: 1310-1316
18 **Reddy SK**, Pawlik TM, Zorzi D, Gleisner AL, Ribero D, Assumpcao L, Barbas AS, Abdalla EK, Choti MA, Vauthey JN, Ludwig KA, Mantyh CR, Morse MA, Clary BM. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. *Ann Surg Oncol* 2007; **14**: 3481-3491
19 **Chen J**, Li Q, Wang C, Zhu H, Shi Y, Zhao G. Simultaneous vs. staged resection for synchronous colorectal liver metastases: a metaanalysis. *Int J Colorectal Dis* 2011; **26**: 191-199
20 **Capussotti L**, Ferrero A, Viganò L, Ribero D, Lo Tesoriere R, Polastri R. Major liver resections synchronous with colorectal surgery. *Ann Surg Oncol* 2007; **14**: 195-201
21 **Luo Y**, Wang L, Chen C, Chen D, Huang M, Huang Y, Peng J, Lan P, Cui J, Cai S, Wang J. Simultaneous liver and colorectal resections are safe for synchronous colorectal liver metastases. *J Gastrointest Surg* 2010; **14**: 1974-1980
22 **Thelen A**, Jonas S, Benckert C, Spinelli A, Lopez-Hänninen E, Rudolph B, Neumann U, Neuhaus P. Simultaneous versus staged liver resection of synchronous liver metastases from colorectal cancer. *Int J Colorectal Dis* 2007; **22**: 1269-1276
23 **de Santibañes E**, Fernandez D, Vaccaro C, Quintana GO, Bonadeo F, Pekolj J, Bonofiglio C, Molmenti E. Short-term and long-term outcomes after simultaneous resection of colorectal malignancies and synchronous liver metastases. *World J Surg* 2010; **34**: 2133-2140
24 **Lambert LA**, Colacchio TA, Barth RJ. Interval hepatic resection of colorectal metastases improves patient selection. *Arch Surg* 2000; **135**: 473-479; discussion 479-480
25 **Yoshidome H**, Kimura F, Shimizu H, Ohtsuka M, Kato A, Yoshitomi H, Furukawa K, Mitsuhashi N, Takeuchi D, Iida A, Miyazaki M. Interval period tumor progression: does delayed hepatectomy detect occult metastases in synchronous colorectal liver metastases? *J Gastrointest Surg* 2008; **12**: 1391-1398
26 **Nordlinger B**, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Collette L, Praet M, Bethe U, Van Cutsem E, Scheithauer W, Gruenberger T. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008; **371**: 1007-1016
27 **Allen PJ**, Kemeny N, Jarnagin W, DeMatteo R, Blumgart L, Fong Y. Importance of response to neoadjuvant chemotherapy in patients undergoing resection of synchronous colorectal liver metastases. *J Gastrointest Surg* 2003; **7**: 109-115; discussion 116-117
28 **Reddy SK**, Zorzi D, Lum YW, Barbas AS, Pawlik TM, Ribero D, Abdalla EK, Choti MA, Kemp C, Vauthey JN, Morse MA, White RR, Clary BM. Timing of multimodality therapy for resectable synchronous colorectal liver metastases: a retrospective multi-institutional analysis. *Ann Surg Oncol* 2009; **16**: 1809-1819
29 **Minagawa M**, Yamamoto J, Miwa S, Sakamoto Y, Kokudo N, Kosuge T, Miyagawa S, Makuuchi M. Selection criteria for simultaneous resection in patients with synchronous liver metastasis. *Arch Surg* 2006; **141**: 1006-1012; discussion 1013
30 **Capussotti L**, Vigano' L, Ferrero A, Lo Tesoriere R, Ribero D, Polastri R. Timing of resection of liver metastases synchronous to colorectal tumor: proposal of prognosis-based decisional model. *Ann Surg Oncol* 2007; **14**: 1143-1150
31 **Mella J**, Biffin A, Radcliffe AG, Stamatakis JD, Steele RJ. Population-based audit of colorectal cancer management in two UK health regions. Colorectal Cancer Working Group, Royal College of Surgeons of England Clinical Epidemiology and Audit Unit. *Br J Surg* 1997; **84**: 1731-1736
32 **Temple LK**, Hsieh L, Wong WD, Saltz L, Schrag D. Use of surgery among elderly patients with stage IV colorectal cancer. *J Clin Oncol* 2004; **22**: 3475-3484
33 **de Haas RJ**, Adam R, Wicherts DA, Azoulay D, Bismuth H, Vibert E, Salloum C, Perdigao F, Benkabbou A, Castaing D. Comparison of simultaneous or delayed liver surgery for limited synchronous colorectal metastases. *Br J Surg* 2010; **97**: 1279-1289
34 **Scoggins CR**, Meszoely IM, Blanke CD, Beauchamp RD, Leach SD. Nonoperative management of primary colorectal cancer in patients with stage IV disease. *Ann Surg Oncol* 1999;

6: 651-657
35 **Sarela AI**, Guthrie JA, Seymour MT, Ride E, Guillou PJ, O' Riordain DS. Non-operative management of the primary tumour in patients with incurable stage IV colorectal cancer. *Br J Surg* 2001; **88**: 1352-1356
36 **Tebbutt NC**, Norman AR, Cunningham D, Hill ME, Tait D, Oates J, Livingston S, Andreyev J. Intestinal complications after chemotherapy for patients with unresected primary colorectal cancer and synchronous metastases. *Gut* 2003; **52**: 568-573
37 **Benoist S**, Pautrat K, Mitry E, Rougier P, Penna C, Nordlinger B. Treatment strategy for patients with colorectal cancer and synchronous irresectable liver metastases. *Br J Surg* 2005; **92**: 1155-1160
38 **Muratore A**, Zorzi D, Bouzari H, Amisano M, Massucco P, Sperti E, Capussotti L. Asymptomatic colorectal cancer with un-resectable liver metastases: immediate colorectal resection or up-front systemic chemotherapy? *Ann Surg Oncol* 2007; **14**: 766-770
39 **Poultsides GA**, Servais EL, Saltz LB, Patil S, Kemeny NE, Guillem JG, Weiser M, Temple LK, Wong WD, Paty PB. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. *J Clin Oncol* 2009; **27**: 3379-3384
40 **Karoui M**, Roudot-Thoraval F, Mesli F, Mitry E, Aparicio T, Des Guetz G, Louvet C, Landi B, Tiret E, Sobhani I. Primary colectomy in patients with stage IV colon cancer and unresectable distant metastases improves overall survival: results of a multicentric study. *Dis Colon Rectum* 2011; **54**: 930-938
41 **Karoui M**, Soprani A, Charachon A, Delbaldo C, Vigano L, Luciani A, Cherqui D. Primary chemotherapy with or without colonic stent for management of irresectable stage IV colorectal cancer. *Eur J Surg Oncol* 2010; **36**: 58-64
42 **Kapiteijn E**, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Rutten HJ, Pahlman L, Glimelius B, van Krieken JH, Leer JW, van de Velde CJ. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; **345**: 638-646
43 **Bosset JF**, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, Bardet E, Beny A, Ollier JC. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; **355**: 1114-1123
44 **Benoist S**. [Recommendations for clinical practice. Therapeutic choices for rectal cancer. How should rectal cancers with synchronous metastases be managed?]. *Gastroenterol Clin Biol* 2007; **31** Spec No 1: 1S75-S80, S100-S102
45 **Mentha G**, Majno PE, Andres A, Rubbia-Brandt L, Morel P, Roth AD. Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary. *Br J Surg* 2006; **93**: 872-878
46 **Viganò L**, Karoui M, Ferrero A, Tayar C, Cherqui D, Capussotti L. Locally advanced mid/low rectal cancer with synchronous liver metastases. *World J Surg* 2011; **35**: 2788-2795

S- Editor Jia F **L- Editor** A **E- Editor** Zheng XM

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
doi:10.4254/wjh.v4.i8.242

World J Hepatol 2012 August 27; 4(8): 242-247
ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Relationship between vitamin D and IL-23, IL-17 and macrophage chemoattractant protein-1 as markers of fibrosis in hepatitis C virus Egyptians

Noha M El Husseiny, Hala M Fahmy, Waleed A Mohamed, Hisham H Amin

Noha M El Husseiny, Hala M Fahmy, Internal Medicine Department, Faculty of Medicine, Cairo University, Cairo 11111, Egypt
Waleed A Mohamed, Department of Chemistry, Cairo University, Cairo 12534, Egypt
Hisham H Amin, Clinical Pathology Department, Faculty of Medicine AL Azhar University, Cairo 15533, Egypt
Author contributions: El Husseiny NM did the statistics and wrote the manuscript; Mohamed WA put the idea of the research, collected the data and did the laboratory work; Fahmy HM participated in the idea of the research and participated in writing the manuscript; Amin HH participated in the laboratory work and data collection.
Correspondence to: Noha M El Husseiny, MD, Department of Internal Medicine, Faculty of Medicine, Cairo University, Cairo 11111, Egypt. dr_noha2002@yahoo.com
Telephone: +20-100-6803571 Fax: +20-223-667260
Received: January 1, 2012 Revised: August 6, 2012
Accepted: August 23, 2012
Published online: August 27, 2012

Abstract

AIM: To assess vitamin D in hepatitis C patients and its relationship to interleukin (IL)-23, IL-17, and macrophage chemoattractant protein-1 (MCP-1).

METHODS: The study was conducted on 50 Egyptian hepatitis C virus (HCV) genotype number IV-infected patients and 25 age- and gender-matched healthy subjects. Venous blood samples were obtained. Samples were allowed to clot and sera were separated by centrifugation and stored at -20 ℃. A 25 hydroxy vitamin D assay was carried out using solid phase RIA. A 1,25 dihydroxy vitamin D assay was carried out using a commercial kit purchased from Incstar Corporation. IL-17 and -23 and MCP-1 were assayed by an enzyme immunoassay. Quantitative and qualitative polymerase chain reaction for HCV virus were done by TaqMan technology. Only HCV genotype IV-infected subjects were included in the study. The mean ± SD were determined, a *t*-test for comparison of means of different parameters was used. Correlation analysis was done using Pearson's correlation. Differences among different groups were determined using the Kruskal-Wallis test.

RESULTS: The mean vitamin D level in HCV patients (group Ⅰ) was 15 ± 5.2 ng/mL while in control (group Ⅱ) was 39.7 ± 10.8. For active vitamin D in group Ⅰ as 16.6 ± 4.8 ng/mL while in group Ⅱ was 41.9 ± 7.9. IL-23 was 154 ± 97.8 in group Ⅰ and 6.7 ± 2.17 in group Ⅱ. IL-17 was 70.7 ± 72.5 in cases and 1.2 ± 0.4 in control. MCP-1 was 1582 ± 794.4 in group Ⅰ and 216.1 ± 5.38 in group Ⅱ. Vitamin D deficiency affected 72% of HCV-infected patients and 0% of the control group. Vitamin D insufficiency existed in 28% of HCV-infected patients and 12% of the control group. One hundred percent of the cirrhotic patients and 40% of non cirrhotic HCV-infected patients had vitamin D deficiency. IL-23, IL-17, and MCP-1 were markedly increased in HCV-infected patients in comparison to controls.A significant negative correlation between vitamin D and IL-17 and -23 and MCP-1 was detected. HCV-infected males and females showed no differences with respect to viral load, vitamin D levels, IL-17, IL-23 and MCP-1. The viral load was negatively correlated with vitamin D and active vitamin D (P = 0.0001 and P = 0.001, respectively), while positively correlated with IL-23, IL-17, and MCP-1. We classified the patients according to sonar findings into four groups. Group Ⅰa with bright hepatomegaly and included 14 patients. Group Ⅰb with perihepatic fibrosis and included 11 patients. Group Ⅰc with liver cirrhosis and included 11 patients. Group Ⅰd with hepatocellular carcinoma (HCC) and included 14 patients. Vitamin D and active vitamin D were shown to be lower in cirrhotic patients and much lower in patients with HCC, and this difference was highly significant (P = 0.0001). IL-17 and -23 and MCP-1 were higher in advanced liver disease) and the differences were highly significant (P = 0.0001).

CONCLUSION: Whether the deficiency of vitamin D is related to HCV-induced chronic liver disease or predisposing factor for higher viral load is a matter of debate.

Key words: Vitamin D; Macrophage chemoattractant protin-1; Liver cirrhosis; Interleukin-23; Interleukin-17; Liver cirrhosis

Peer reviewers: Yasemin Hatice Balaban, Professor, Hacettepe University, Medical Faculty Internal Medicine Department, Gastroenterology Unit, Ankara 06100, Turkey; Ajith TA, PhD, Assistant Professor of Biochemistry, Department of Biochemistry, Amala Institute of Medical Sciences, Amala Nagar, Thrissur, 680 555, India

El Husseiny NM, Fahmy HM, Mohamed WA, Amin HH. Relationship between vitamin D and IL-23, IL-17 and macrophage chemoattractant protein-1 as markers of fibrosis in hepatitis C virus Egyptians. *World J Hepatol* 2012; 4(8): 242-247 Available from: URL: http://www.wjgnet.com/1948-5182/full/v4/i8/242.htm DOI: http://dx.doi.org/10.4254/wjh.v4.i8.242

INTRODUCTION

Vitamin D is a critical regulator of immunity, playing a role in both innate and cell-mediated immune responses. Vitamin D suppresses the production of T helper (Th)1 cytokines, such as interferon-γ (IFN-γ) and interleukin (IL)-2, and consequently leads to enhanced production of Th2 cytokines, such as IL-4 and -5, thus potentially promoting humoral immune responses. Vitamin D also promotes innate immunity by directly inducing the gene expression of antimicrobial peptides (cathelicidin and β-defensin 2) in various human cell types[1-4].

Vitamin D deficiency has been shown to be associated with several immune-mediated diseases, and susceptibility to infection and cancer. In fact, a 25(OH)D concentration < 50 nmol/L (20 ng/mL) is an indication of vitamin D deficiency, whereas a 25(OH)D concentration of 51-74 nmol/L (21-29 ng/mL) is considered to indicate insufficiency[5,6]

IL-23, in conjunction with IL-6 and transforming growth factor β (TGF-β), stimulates the differentiation of Th17 cells with subsequent production of IL-17[7]. IL-17 is a cytokine that acts as a potent mediator in delayed-type reactions by increasing chemokine production in various tissues to recruit monocytes and neutrophils to the site of inflammation, similar to IFN-γ. IL-17 acts synergistically with tumor necrosis factor (TNF) and IL-1[8].

Chronic hepatic cirrhotic patients with genotype 1 have low 25(OH)D serum levels. Low vitamin D is linked to severe fibrosis and a low sustained virologic response (SVR) on IFN-based therapy[9,10].

There is interesting preliminary data that indicate that 1,25(OH)$_2$D3 suppresses Th17 driven cytokine responses, induces Treg cells, induces IL-4 production (Th2) and enhances natural killer T-cell function; differentiation and maturation of B cells is also inhibited. In addition, treatment with vitamin D receptor (VDR) agonists inhibits the T-cell production of IL-17. Furthermore, IL-17 production is sustained by IL-23, an IL-12 family member, the latter of which is strongly inhibited by VDR agonists[11].

Also, 1,25(OH)$_2$D3 has been shown to inhibit macrophage chemoattractant protein-1 (MCP-1)-driven inflammatory process by blocking nuclear factor-κB activation. MCP-1 is expressed in injury and inflammation and leads to direct macrophage recruitment[12].

Hepatitis C virus (HCV) is remarkably efficient at establishing persistent infections, suggesting that HCV has evolved one or more strategies aimed at evading the host immune response. T cell responses, including IFN-γ production, are severely suppressed in patients with chronic HCV infections[13].

Aim of the study: To assess the relationship between vitamin D and markers of inflammation in HCV infected patients and measure the degree of this relation to viral load and degree of fibrosis.

MATERIALS AND METHODS

The study approved by Ethical Committee. The study included 50 patients with HCV-related chronic liver disease with a minimum duration of 7 years (group Ⅰ), who attended the Hepatology Outpatient Clinic, Endemic Disease Hospital, Faculty of Medicine, Cairo University.

Collection of patients required 4 mo. Inclusion criteria were based on previous history of liver disease with HCV infection of both sexes, whether new patients or under follow up were included. Isolated HBV or coinfection with HBV and HIV infected patients were excluded.

Group Ⅰ included 36 males (72%) and 14 females (28%), ranging in age from 30-65 years, with a mean age of 47.5 years. Twenty-five age- and gender-matched healthy subjects were included as a control group (group Ⅱ). The controls had liver functions and abdominal U/S and test for HCV antibodies which were all normal. Informed consent was obtained from the patients and controls regarding all the procedures done.

All patients were subjected to thorough history-taking and a clinical examination. Abdominal ultrasonography was performed on all patients, and according to the results, patients were classified into 4 subgroups as follows: 14 patients with bright hepatomegly; 11 patients with perihepatic fibrosis; 11 patients with hepatic cirrhosis; and14 patients with hepatocellular carcinoma (HCC) and cirrhosis.

Venous blood samples were obtained after overnight fasting from all patients. Samples were allowed to clot and sera were separated by centrifugation and stored at -20 ℃.

A 25 hydroxy vitamin D assay was carried out using a commercial kit purchased from (Medgenix Diagnostics S.A. Zoning Industrial. B-6220 Fleurus, Belgium; Mawer,

1980) using solid phase RIA. A 1,25 dihydroxy vitamin D assay was carried out using a commercial kit purchased from Incstar Corporation (Stillwater, MN USA; Hollis, 1986). IL-17 and -23 and MCP-1 were assayed by an enzyme immunoassay (Biosource Europe S.A). Quantitative and qualitative PCR for HCV virus were done by TaqMan technology. Only HCV genotype IV-infected subjects were included in the study.

Statistics

SPSS (version 15) was used for statistic measures of this study. The mean ± SD were determined, a *t*-test for comparison of means of different parameters was used. Correlation analysis was done using Pearson's correlation. Differences among different groups were determined using the Kruskal-Wallis test.

RESULTS

Vitamin D deficiency, defined as a serum vitamin D level < 20 ng/mL, was present in 36 patients (72%) and none (0%) of the control group. Vitamin D insufficiency (20-29 ng/mL) existed in 14 (28%), HCV-infected patients and 3 (12%) subjects in the control group. Furthermore, 25 (100%) cirrhotic patients had vitamin D deficiency and 10 (40%) non-cirrhotic HCV-infected cases. Table 1 shows the laboratory data of the study groups and demonstrates a statistically significant difference with respect to vitamin D and its active form, IL-23, and IL-17 between both groups. The viral load mean was 128 000 ± 28 000 IU/mL.

Table 2 demonstrates the correlation between different parameters in HCV-infected subjects and controls. There was significant negative correlation between vitamin D and viral load, IL-23, IL-17 and MCP-1. Meanwhile there was a positive correlation between viral load and IL-17, IL-23 and MCP-1. Table 3 shows the studied parameters in HCV-infected patients when classified into 2 subgroups according to gender. Figure 1 show correlations between vitamin D and IL-23, IL-17, and viral load, respectively. Table 4 demonstrates the laboratory data in the four subgroups of HCV-infected patients. Vitamin D and active vitamin D were shown to be lower in cirrhotic patients and much lower in patients with HCC, and this difference was highly significant ($P = 0.0001$). IL-17 and -23 and MCP-1 were higher in advanced liver disease) and the differences were highly significant ($P = 0.0001$)

Table 1 Laboratory data of study groups

Item	Group Ⅰ (HCV infected subjects)	Group Ⅱ (controls)
25(OH) vit D (ng/mL)	15 ± 5.2[a]	39.7 ± 10.8
1,25(OH) vit D (ng/mL)	16.6 ± 4.8[a]	41.9 ± 7.9
IL-23 (ng/mL)	154 ± 97.8[a]	6.7 ± 2.17
IL-17 (ng/mL)	70.7 ± 72.5[a]	1.2 ± 0.4
MCP-1 (ng/mL)	1582 ± 794.4[a]	216.1 ± 5.38

[a]$P < 0.0002$. Vit: Vitamin; IL: Interleukin; HCV: Hepatitis C virus; MCP-1: Macrophage chemoattractant protein-1.

Table 2 Correlations between different parameters in hepatitis C virus infected subjects

Items	R	*P* value
Vit D, viral load	-0.84	0.000
Active D, viral load	-0.846	0.000
Vit D and IL-23	-0.776	0.000
Active D and IL-23	-0.801	0.000
Vit D and IL-17	-0.665	0.000
Active D and IL-17	-0.679	0.000
IL-17 and viral load	0.951	0.000
IL-23 and viral load	0.922	0.000
MCP-1 and viral load	0.94	0.000
MCP-1 and vitamin D	-0.94	0.000
MCP-1 and active D	-0.92	0.000

Vit: Vitamin; IL: Interleukin; MCP-1: Macrophage chemoattractant protein-1.

Table 3 Differences between male and female subgroups of the hepatitis C virus infected patients

Item	Male group (n = 27)	Female group (n = 23)	*P* value
Vit D (ng/mL)	15.0 ± 5.12910	15.0 ± 5.6	1
Active vit D (ng/mL)	16.6 ± 4.5	16.6 ± 5.3	0.96
Viral load (IU/mL)	126.8 ± 98.6	129.3 ± 102.6	0.93
IL-23 (ng/mL)	152.4 ± 96.6	156.1 ± 101.3	0.92
IL-17 (ng/mL)	69.8 ± 69.2	71.9 ± 77.6	0.9
MCP-1 (ng/mL)	1575.7 ± 765.4	1589.4 ± 844.5	0.9

Vit: Vitamin; IL: Interleukin; MCP-1: Macrophage chemoattractant protein-1.

DISCUSSION

The liver plays a central role in vitamin D metabolism. Vitamin D inadequacy is common in non-cholestatic chronic liver diseases and correlates with disease severity. The current study showed a significant reduction of vitamin D and its active metabolites in HCV genotype 4-infected patients compared to healthy controls. This reduction was more prevalent and severe in cirrhotic *vs* non-cirrhotic patients. This is consistent with previous studies done on patients with genotype 1, which showed that vitamin D deficiency is universal (92%) among patients with chronic liver disease, and at least one-third of the patients have severe vitamin D deficiency[14-16].

Our results showed that IL-23 and -17 were markedly increased in HCV-infected patients in comparison to controls. Regulation of Th1 and Th17 responses in HCV-infected individuals was studied, and it was reported that TGF-β and IL-6 promote differentiation of naive murine $CD4^+$ T cells into IL-17-secreting Th17 cells. In addition, it has been reported that other innate cytokines, including IL-1, IL-23, TNF-α, and IL-21, in different combinations or with TGF-β, are also involved in differentiation, amplification, or stabilization of the Th17 phenotype[17,18].

Table 4 Laboratory data in the four subgroups of hepatitis C virus infected subjects

Item	Group Ⅰa (bright hepatomegaly) (*n* = 14)	Group Ⅰb (perihepatic fibrosis) (*n* = 11)	Group Ⅰc (liver cirrhosis) (*n* = 11)	Group Ⅰd (HCC) (*n* = 14)	Normal (*n* = 25)	*P* value
IL-17 (ng/mL)	7.6	5.1	115.9	150.3	1.26	0.000
IL-23 (ng/mL)	76.8	51.2	259.3	225.9	6.7	0.000
Vit D (ng/mL)	19.8	19.4	10.9	9.7	39.1	0.000
Active vit D (ng/mL)	20.6	21	13	11.7	41.1	0.000
Viral load (IU/mL)	66.3	42.4	165.1	231.1	0	0.000
MCP-1 (ng/mL)	910.3	838.8	2090.9	2448	237.34	0.000

Vit: Vitamin; IL: Interleukin; MCP-1: Macrophage chemoattractant protein-1; HCC: Hepatocellular carcinoma.

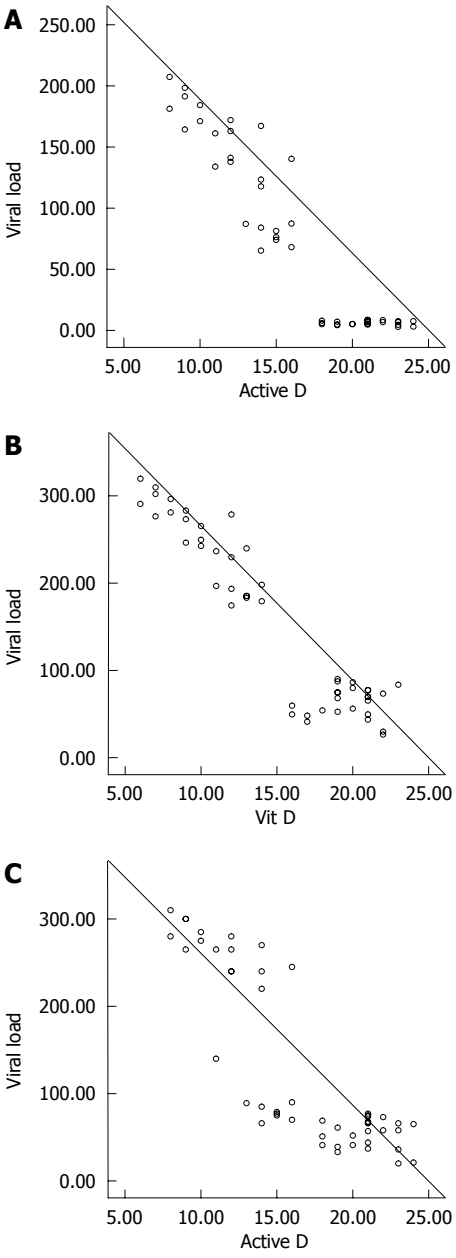


Figure 1 Correlation between vitamin D (ng/mL) and interleukin-17 (ng/mL) (A), interleukin-23 (B) and viral load (C).

Our study reported that there is a significant negative correlation between vitamin D and IL-17 and -23. Previous studies on mice showed that vitamin D is a strong inhibitor of Th17 polarization and Th17 cytokine expression of splenic CD4+ T cells. Furthermore, Th17 differentiation from naïve T cells was affected by vitamin D. These data implicate a regulatory mechanism on Th17 cells by vitamin D, through the reduction of RORgt expression[19].

The effect of vitamin D on the behavior of Th17 cells was investigated in different diseases and it was found that vitamin D suppressed the expression of IL-17 and -23[20-23].

We reported a positive correlation between IL-23 and -17 with viral load, a finding which further support our suggestion regarding the link between vitamin D and both IL-17 and -23 in immune regulation in HCV genotype IV-related chronic liver disease. These findings may support our suggestion that increased IL-17 and -23 could be, at least in part, involved in the role of vitamin D in the immune response in HCV genotype IV-related liver disease and explain how vitamin D deficiency plays a role in increasing liver fibrosis.

Our results revealed HCV-infected males and females had no differences with respect to vitamin D levels. In contrast with our results, Arteh *et al*[24] who reported that African American females with chronic liver disease are at higher risk of vitamin D deficiency.

Our study showed that the viral load mean value was $1.28 \times 10^5 \pm 28 \times 10^3$ IU/mL. A significant negative correlation was reported between vitamin D and active vitamin D and viral load ($P = 0.0001$ and $P = 0.001$, respectively).

Vitamin D is an important immune modulator and preliminary data indicated an association between vitamin D deficiency and SVR rates in HCV as reduced 25-hydroxyvitamin D levels and CYPB27-1260 promotor polymorphism with reduced 1,25-dihydroxyvitamin D levels are associated with failure to achieve SVR in HCV genotypes 1-, 2-, and 3-infected patients[9,25]. Our HCV patients with genotype IV need further follow up to confirm the effect of vitamin D deficiency on their responses to treatment.

There was a significant increase in level of MCP-1 in our patients with all grades of hepatic affection in comparison to controls. Similar results were reported by Camps *et al*[26]. However, Panasiuk *et al*[27] reported a de-

crease in the MCP-1 level in liver cirrhosis in comparison to the controls and did not reflect any inflammatory process in liver cirrhosis. More studies are needed to explore this point of controversy.

Our results also revealed a significant negative correlation between vitamin D and MCP-1. This supports the role of decreased vitamin D in inflammation and fibrosis. No previous work in hepatic patients studied this relationship. However, Zehnder *et al*[28] reported that reduction of the vitamin D hormonal system in kidney disease was associated with increased renal inflammation and fibrosis. Zehnder *et al*[28] reported a significant negative correlation between vitamin D and MCP-1. Logistic regression analysis with urinary MCP-1 as a binary outcome showed that a 10-unit increase in serum 1,25(OH)$_2$D or 25OHD resulted in lower renal inflammation[28].

On classifying HCV-infected patients according to sonar finding into four groups, vitamin D and active vitamin D were shown to be lower in cirrhotic patients and much lower in patients with HCC, and this difference was highly significant (P = 0.0001). IL-17 and -23 and MCP-1 were higher in advanced liver disease) and the differences were highly significant (P = 0.0001). These findings are concomitant with previous results which indicate that vitamin D inadequacy is common in non-cholestatic chronic liver diseases and correlates with disease severity[14]. The difference in viral load among these groups may explain in part the difference in levels of inflammatory cytokines.

In conclusion, vitamin D deficiency is prevalent in HCV genotype IV-infected patients and viral load is negatively correlated to vitamin D. Whether or not this deficiency is related to HCV-induced chronic liver disease or predisposing factor for higher viral load is a matter of debate. In view of the immune function of vitamin D, vitamin D status may be assessed and supplements may be considered to achieve a SVR with IFN-based therapy. The negative correlation between vitamin D and IL-23 and -17 and MCP-1 may highlight, at least in part, how these cytokines might be involved with vitamin D in immune responses in HCV genotype IV-related liver disease and may explain how vitamin D deficiency plays a role in increasing liver fibrosis.

ACKNOWLEDGMENTS

Special thanks to workers at the Hepatology Clinic of Kasr El Eini-Cairo University for their help during this research.

COMMENTS

Background

Vitamin D receptor (VDR) is found in significant concentrations in the T lymphocyte and macrophage populations. However, the highest concentration of VDR is in the immature immune cells of the thymus and the mature CD-8 T lymphocytes.

Research frontiers

This study highlights the relationship between interleukin (IL)-23, IL-17 and macrophage chemoattractant protein-1 (MCP-1) with vitamin D in patients with hepatitis C virus (HCV).

Innovations and breakthroughs

In view of the immune function of vitamin D, vitamin D status may be assessed and supplements may be considered to achieve a sustained virologic response with interferon-based therapy. The negative correlation between vitamin D and IL-23 and -17 and MCP-1 may highlight, at least in part, how these cytokines might be involved with vitamin D in immune responses in HCV genotype IV-related liver disease and may explain how vitamin D deficiency plays a role in increasing liver fibrosis.

Applications

IL-23, IL-17 and MCP-1 can be used as markers of degree of liver fibrosis. Vitamin D supplements may improve immune response and delays fibrosis induced by HCV.

Peer review

Authors studied the relation between serum vitamin D levels and HCV related liver disease. They detected a strong correlation with severity fibrosis, treatment response and cytokine levels which has been also shown previously.

REFERENCES

1 **Shirakawa AK**, Nagakubo D, Hieshima K, Nakayama T, Jin Z, Yoshie O. 1,25-dihydroxyvitamin D3 induces CCR10 expression in terminally differentiating human B cells. *J Immunol* 2008; **180**: 2786-2795
2 **Deluca HF**, Cantorna MT. Vitamin D: its role and uses in immunology. *FASEB J* 2001; **15**: 2579-2585
3 **Mahon BD**, Wittke A, Weaver V, Cantorna MT. The targets of vitamin D depend on the differentiation and activation status of CD4 positive T cells. *J Cell Biochem* 2003; **89**: 922-932
4 **Muller K**, Svenson M, Bendtzen K. 1 alpha,25-Dihydroxyvitamin D3 and a novel vitamin D analogue MC 903 are potent inhibitors of human interleukin 1 in vitro. *Immunol Lett* 1988; **17**: 361-365
5 **Lange NE**, Litonjua A, Hawrylowicz CM, Weiss S. Vitamin D, the immune system and asthma. *Expert Rev Clin Immunol* 2009; **5**: 693-702
6 **Holick MF**, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr* 2008; **87**: 1080S-1086S
7 **McGeachy MJ**, Cua DJ. Th17 cell differentiation: the long and winding road. *Immunity* 2008; **28**: 445-453
8 **Miossec P**, Korn T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. *N Engl J Med* 2009; **361**: 888-898
9 **Petta S**, Cammà C, Scazzone C, Tripodo C, Di Marco V, Bono A, Cabibi D, Licata G, Porcasi R, Marchesini G, Craxí A. Low vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. *Hepatology* 2010; **51**: 1158-1167
10 **Mouch SA**, Fireman Z, Jarchovsky J, Assy N. Vitamin D supplement improve SVR in chronic hepatitis C (genotype 1) Naïve patients treated with Peg interferon and ribavirin. EASL 45th Annual Meeting of European Association for the Study of the Liver; 2010 Apr 14-18; Vienna, Austria
11 **Steinman L**. A brief history of T(H)17, the first major revision in the T(H)1/T(H)2 hypothesis of T cell-mediated tissue damage. *Nat Med* 2007; **13**: 139-145
12 **Eardley KS**, Kubal C, Zehnder D, Quinkler M, Lepenies J, Savage CO, Howie AJ, Kaur K, Cooper MS, Adu D, Cockwell P. The role of capillary density, macrophage infiltration and interstitial scarring in the pathogenesis of human chronic kidney disease. *Kidney Int* 2008; **74**: 495-504
13 **Eisen-Vandervelde AL**, Waggoner SN, Yao ZQ, Cale EM, Hahn CS, Hahn YS. Hepatitis C virus core selectively suppresses interleukin-12 synthesis in human macrophages by interfering with AP-1 activation. *J Biol Chem* 2004; **279**: 43479-43486
14 **Fisher L**, Fisher A. Vitamin D and parathyroid hormone in outpatients with noncholestatic chronic liver disease. *Clin*

Gastroenterol Hepatol 2007; **5**: 513-520
15 **Bouillon R**, Auwerx J, Dekeyser L, Fevery J, Lissens W, De Moor P. Serum vitamin D metabolites and their binding protein in patients with liver cirrhosis. *J Clin Endocrinol Metab* 1984; **59**: 86-89
16 **Duarte MP**, Farias ML, Coelho HS, Mendonça LM, Stabnov LM, do Carmo d Oliveira M, Lamy RA, Oliveira DS. Calcium-parathyroid hormone-vitamin D axis and metabolic bone disease in chronic viral liver disease. *J Gastroenterol Hepatol* 2001; **16**: 1022-1027
17 **Rowan AG**, Fletcher JM, Ryan EJ, Moran B, Hegarty JE, O' Farrelly C, Mills KH. Hepatitis C virus-specific Th17 cells are suppressed by virus-induced TGF-beta. *J Immunol* 2008; **181**: 4485-4494
18 **Mills KH**. Induction, function and regulation of IL-17-producing T cells. *Eur J Immunol* 2008; **38**: 2636-2649
19 **Mus AM**, van Hamburg JP, Asmawidjaja P, Hazes JMW, van Leeuwen H, Boon L, Colin E. Vitamin D suppresses Th17 cytokines via down regulation of RORgammat and NFATC2 and by differential regulation of GATA3. *Arthritis Rheum* 2010; **62** Suppl 10: 38
20 **van Hamburg JP**, Asmawidjaja PS, Davelaar N, Cornelissen FC, Mus AMC, Bakx PAGM, Colin EM, van Leeuwen H, Hazes JMW, Dolhain RJEM, Lubberts E. Vitamin D suppresses the pathogenic behaviour of primary Th17 cells from patients with early rheumatoid arthritis. *Ann Rheum Dis* 2011; **70**: A47
21 **Bermejo-Martin JF**, Ortiz de Lejarazu R, Pumarola T, Rello J, Almansa R, Ramírez P, Martin-Loeches I, Varillas D, Gallegos MC, Serón C, Micheloud D, Gomez JM, Tenorio-Abreu A, Ramos MJ, Molina ML, Huidobro S, Sanchez E, Gordón M, Fernández V, Del Castillo A, Marcos MA, Villanueva B, López CJ, Rodríguez-Domínguez M, Galan JC, Cantón R, Lietor A, Rojo S, Eiros JM, Hinojosa C, Gonzalez I, Torner N, Banner D, Leon A, Cuesta P, Rowe T, Kelvin DJ. Th1 and Th17 hypercytokinemia as early host response signature in severe pandemic influenza. *Crit Care* 2009; **13**: R201
22 **Zold E**, Szodoray P, Kappelmayer J, Gaal J, Csathy L, Barath S, Gyimesi E, Hajas A, Zeher M, Szegedi G, Bodolay E. Impaired regulatory T-cell homeostasis due to vitamin D deficiency in undifferentiated connective tissue disease. *Scand J Rheumatol* 2010; **39**: 490-497
23 **Bartosik-Psujek H**, Tabarkiewicz J, Pocinska K, Stelmasiak Z, Rolinski J. Immunomodulatory effects of vitamin D on monocyte-derived dendritic cells in multiple sclerosis. *Mult Scler* 2010; **16**: 1513-1516
24 **Arteh J**, Narra S, Nair S. Prevalence of vitamin D deficiency in chronic liver disease. *Dig Dis Sci* 2010; **55**: 2624-2628
25 **Lange CM**, Bojunga J, Ramos-Lopez E, von Wagner M, Hassler A, Vermehren J, Herrmann E, Badenhoop K, Zeuzem S, Sarrazin C. Vitamin D deficiency and a CYP27B1-1260 promoter polymorphism are associated with chronic hepatitis C and poor response to interferon-alfa based therapy. *J Hepatol* 2011; **54**: 887-893
26 **Camps J**, Marsillach J, Rull A, Alonso-Villaverde C, Joven J. Interrelationships between paraoxonase-1 and monocyte chemoattractant protein-1 in the regulation of hepatic inflammation. *Adv Exp Med Biol* 2010; **660**: 5-18
27 **Panasiuk A**, Zak J, Kasprzycka E, Janicka K, Prokopowicz D. Blood platelet and monocyte activations and relation to stages of liver cirrhosis. *World J Gastroenterol* 2005; **11**: 2754-2758
28 **Zehnder D**, Quinkler M, Eardley KS, Bland R, Lepenies J, Hughes SV, Raymond NT, Howie AJ, Cockwell P, Stewart PM, Hewison M. Reduction of the vitamin D hormonal system in kidney disease is associated with increased renal inflammation. *Kidney Int* 2008; **74**: 1343-1353

S- Editor Jia F **L- Editor** A **E- Editor** Zheng XM

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
doi:10.4254/wjh.v4.i8.248

World J Hepatol 2012 August 27; 4(8): 248-251
ISSN 1948-5182 (online)

CASE REPORT

A rare cause of drug-induced hepatitis in an immunocompromised patient and the role of glutathione

Viplove Senadhi, Deepika Arora, Manish Arora, Franklin Marsh

Viplove Senadhi, Division of Gastroenterology and Hepatology and Brater Scholar, Indiana Institute for Personalized Medicine, Indiana University School of Medicine, Indianapolis, IN 46202, United States
Deepika Arora, Elmhurst Hospital/Mount Sinai School of Medicine, New York City, New York, NY 10005, United States
Manish Arora, Division of Gastroenterology and Hepatology, University of Maryland and National Institute of Health, Baltimore/Washington DC, MD 21742, United States
Franklin Marsh, Division of Gastroenterology and Hepatology, New York Hospital-Weill Cornell Medical Center, New York City, New York, NY 10005, United States
Author contributions: Senadhi V wrote the entire manuscript, performed the literature review, including all references, incorporated it into the manuscript, modified the initial abstract to its final form, modified a poster presentation to its final form, including the table and performed all revisions and editing of the paper; Arora D wrote the initial abstract, constructed the table, created and presented the final poster presentation; Arora M also reviewed the manuscript and incorporated suggestions throughout the abstract and manuscript process; Marsh F was the mentor author and incorporated suggestions throughout the abstract/manuscript process.
Correspondence to: Dr. Viplove Senadhi, Department of Gastroenterology and Hepatology, Indiana University School of Medicine, 1050 Wishard Blvd, RG 4100, Indianapolis, IN 46202, United States. vsenadhi@hotmail.com
Telephone: +1-317-2780402 Fax: +1-678-6235999
Received: January 14, 2011 Revised: June 28, 2012
Accepted: August 23, 2012
Published online: August 27, 2012

Abstract

The Food and Drug Administration (FDA) has issued a warning on numerous herbal drugs, including many popular products at General Nutrition Centers (GNC), regarding unstudied hepatotoxicity. There have been recent reports of GNC products such as hydroxycut and herbalife, causing drug-induced hepatitis. Herbal medications are over-the-counter products and are not investigated thoroughly by the FDA. Given that the most common outpatient laboratory abnormality is elevated liver transaminases, a sign of hepatocellular toxicity; it is not surprising that some of these products end up causing hepatic dysfunction, especially when taken in large volume. There are numerous herbal supplements that are hepatotoxic, however, these medications have a much more significant effect in human immunodeficiency virus (HIV)/ acquired immune deficiency syndrome patients, which is secondary to depleted glutathione. We present a rare case of drug induced hepatitis secondary to herbal medications used to treat HIV and elucidate the role of glutathione depletion in immunocompromised patients.

Key words: Glutathione; Human immunodeficiency virus; Acquired immune deficiency syndrome; Immunocompromised; Drug induced hepatitis; Hepatotoxicity; N-acetylcysteine; Herbal Medications

Peer reviewer: Yasemin Hatice Balaban, Professor, Hacettepe University, Oyak Sitesi no6/2 Cankaya, Ankara 06570, Turkey

Senadhi V, Arora D, Arora M, Marsh F. A rare cause of drug-induced hepatitis in an immunocompromised patient and the role of glutathione. *World J Hepatol* 2012; 4(8): 248-251 Available from: URL: http://www.wjgnet.com/1948-5182/full/v4/i8/248.htm DOI: http://dx.doi.org/10.4254/wjh.v4.i8.248

INTRODUCTION

The Food and Drug Administration (FDA) has issued a warning on numerous herbal drugs, including many popular products at General Nutrition Centers (GNC), regarding unstudied hepatotoxicity. For example, there have been recent reports of GNC products such as Hydroxycut and Herbalife, causing drug-induced hepatitis[1]. Herbal medications are over-the-counter (OTC) products

and are not investigated thoroughly by the FDA. Given that the most common outpatient laboratory abnormality is elevated liver transaminases, a sign of hepatocellular toxicity, it is not surprising that some of these products end up causing hepatic dysfunction, especially when taken in large volume, which will be illustrated in our case presentation. There are numerous herbal supplements that are hepatotoxic (Table 1); however, these medications have a much more significant effect in human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) patients, which is secondary to depleted glutathione[2]. We present a rare case of drug induced hepatitis secondary to herbal medications used to treat HIV and elucidate the role of glutathione depletion in immunocompromised patients.

CASE REPORT

A 26-year-old African American male with a past medical history of HIV, with a recent CD4 count of 301, presented with yellow eye discoloration, dark colored urine, clay colored stools, nausea, malaise and fatigue of 2 wk duration. Pertinent physical examination findings revealed scleral icterus without evidence of anemia, ecchymosis, pruritus, asterixis, encephalopathy, and fetor hepaticus. Abdominal examination revealed non-tender hepatomegaly (liver span 14 cm). Laboratory findings revealed an albumin of 4.1, aspartate aminotransferase (AST) of 1301 (3 wk before AST = 432), alanine aminotransferase (ALT) of 1648 (3 wk before ALT = 609), alkaline phosphatase (ALP) of 154 (3 wk before ALP = 72), serum bilirubin of 10.4 (3 wk before bilirubin = 0.7), and a normal international normalized ratio. An acute hepatitis panel (hepatitis A, B and C) and serum acetaminophen levels were unremarkable. A workup for Autoimmune Hepatitis was also unrevealing. An abdominal computed tomography revealed nonspecific periportal edema and mild hepatomegaly. On further history, the patient was found to have increased his intake of herbal medications from 24 to 48 herbal pills per day, prior to his admission to treat his recently diagnosed HIV. His herbal medications included fucoidan, maya nut, and finger millet, to treat his recently diagnosed HIV. After discontinuation of his herbal HIV medications, his liver functions tests resolved within 2 wk and his symptoms dissipated.

DISCUSSION

Glutathione, a cysteine containing polypeptide, is essential for the function of all cells, but it is especially important in preventing oxidative stress and is involved in inflammatory cascades[2]. Additionally, glutathione becomes pivotal in HIV/AIDS patients[2]. In fact, low glutathione levels are linked with HIV disease progression and poor survival[2]. Glutathione levels are depleted in HIV patients and are correlated with depleted CD4 counts/decreased survival[2]. Thus, AIDS patients, more specifically, those with CD4 counts that are lower than 200, have even lower glutathione levels[2]. The depleted glutathione in HIV/AIDS patients is secondary to multiple mechanisms, such as excessive use of glutathione-depleting drugs, excessive natural production of proinflammatory cytokines such as TNF-α, and HIV gene dysregulation, leading to lower levels of superoxide dismutase[2]. Superoxide dismutase is an enzyme that prevents oxidative stress naturally and enhances the use of the enzyme glucose-6-phosphate dehydrogenase, which maintains glutathione stores[3].

Glutathione stores are critical in the metabolism of toxic free oxygen radicals that are created in drug detoxification[3]. For instance, the mechanism of fulminant hepatic failure in patients with severe acetaminophen overdose is fundamentally due to depleted glutathione stores[3]. Chronic alcoholics also have depleted glutathione stores due to the fact that alcohol directly depletes glutathione stores[2]. Alcohol toxicity is also more dangerous to the liver in the setting of depleted glutathione stores. Thus, this is the reason that alcoholics are more susceptible to free radical damage induced by Tylenol[3]. Similarly, there are many other drugs that can be toxic in the setting of depleted glutathione levels. Our patient had HIV/AIDS and thus, had depleted glutathione levels, which made him more susceptible to drug induced hepatitis.

The mechanism of the drug N-acetylcysteine (NAC) is to augment glutathione reserves in the body, and in combination with glutathione, directly binds to toxic metabolites that are created in drug metabolism[3]. The best example of this mechanism is the treatment of an Acetaminophen (Tylenol) overdose. Tylenol normally creates a toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI), which is toxic to hepatocytes[3]. NAPQI is metabolized by glutathione, but in the setting of depleted glutathione levels (more likely in HIV/AIDS) accumulates to cause severe liver failure[3]. Similarly, this occurs in the metabolism of numerous other drugs as well, especially at higher toxic doses. The American Association for the Study of Liver Diseases recommended NAC for all cases of acute liver failure with exception of liver shock[4]. NAC was shown to improve transplant free survival in patients with early stage acute liver failure[4]. Similarly, NAC administration in HIV patients was shown to increase cysteine levels and thus, increase glutathione levels (cysteine derivative), which is associated with increased survival in HIV/AIDS patients[2]. As discussed above, herbal medications have their toxicities. Our patient was taking herbal medications including maya nut, fucoidan, and finger millet. The hepatotoxicities of these herbal medications are not well known, but in our patient, discontinuation of these medications led to the resolution of his symptoms. It is thought that these medications in tandem in the setting of an HIV/AIDs patient with depleted glutathione levels caused acute liver failure due to a similar mechanism of reduced glutathione levels, with glutathione preventing free radical damage. Finger millet

Table 1 Herbal supplements and their potential hepatoxicities

Herbal supplements	Potential hepatotoxicity
Pyrrolizidine-containing teas	Hepatic veno-occlusive disease
Germander (*Teucrium chamaedrys*)-Diterpenoids	Hepatitis, hepatic cirrhosis
Ma huang (Ephedra products)	Fulminant hepatic failure
Comfrey, Kava Kava, Lipokinetics, Chaparral (*Larrea tridentate*), black cohosh	Hepatotoxicity (rare with black cohosh) Chaparral associated with cholestatic and severe hepatic dysfunction
Panax ginseng (Energy drinks)	Serum transaminitis
St. John's Wort	Interacts with NNRTIs and PIs
European mistletoe	Hepatotoxic drug interactions and serum transaminitis
Saireito (Shosaikoto and goreisan)	Serum transaminitis
Pennyroyal oil (*Mentha pulegium* and *Hedeoma pulegoides* plants)	Direct hepatotoxicity and acute liver failure in higher doses
Fucoidan (Sulfated polysaccharides)	Unknown hepatotoxicity
Maya nut (Finger millet)	Unknown hepatotoxicity

NNRTIs: Non-nucleoside reverse transcriptase inhibitors; PIs: Protease inhibitors.

has been shown to be involved in free radical oxygenation pathways[5].

It is necessary to recognize hepatotoxic medications in any setting, but it is absolutely critical to identify hepatotoxic agents in HIV patients for many reasons. The most compelling reason would be in the setting of an HIV patient on highly active anti-retroviral therapy (HAART). Wrongly attributing hepatotoxicity to proven HAART therapy may subsequently alter the patient's course as well as disease progression. Hepatotoxocity is one of the known side effects of HAART therapy and in some cases, is therapy limiting. HAART, unlike most therapeutic regimens, is specifically tailored to each individual patient based on drug resistance due to viral mutations, comorbidities, patient compliance, patient tolerance to side effects, toxicities, side effects, and disease progression or remission. Thus, it becomes even more monumental to elucidate occult use of herbal or OTC medications that are the true cause of hepatotoxicity and not prematurely discontinue patient tailored HAART therapy. Occult use of herbal medications or OTC medications that cause significant transaminase elevations in the setting of well managed HIV may cause cessation of effective treatment, which may lead to increased viral mutations/drug resistance. However, there are some impediments facing physicians to elucidating herbal medication use. For example, there is a stigma from a patients' perspective that may facilitate concealing use of these medications from their healthcare provider due to the fact that they believe that their healthcare provider will not approve of this "alternative" regimen. Additionally, many patients do not list OTC and herbal medications as documented medications (medications they are taking) when asked by their healthcare provider. Lastly, patients that cease or decrease their HIV treatment (as seen in our patient) in favor of herbal medications; need to be warned of the risk of increased HIV viral mutations.

HIV treatment is further complicated by patient comorbidities such as hepatitis C (30%), hepatitis B (9%), HIV renal disease, and non-compliant patients[6]. Identifying hepatotoxic medications in HIV patients coinfected with Hepatitis C is also crucial. Hepatitis C and HIV coexist 50%-90% of the time in intravenous drug abusers[6]. Thus, another compelling reason to recognize occult herbal medication use and potential hepatotoxic medications is that hepatoxicity would change the treatment regimen in patients with Hepatitis C. Pegylated interferon, the standard of care currently for Hepatitis C, could be limited in the setting of herbal medication use due to possible drug interactions or speculated hepatotoxicity (rare) in the absence of any attributable listed medications of the patient. Thus, treatment would be halted, leading to increased morbidity/mortality in HIV and hepatitis C patients. Even with the addition of the new protease inhibitors, Pegylated interferon is necessary (induction phase) for effective treatment and providers should have a complete understanding of occult use of herbal medications, as potential herbal drug interactions with the protease inhibitors may be therapy limiting.

Identifying hepatotoxic medications in HIV patients coinfected with Hepatitis B is also very important. Hepatitis B and HIV coexist 9% of the time, which is most likely due to the sexual transmission (listed as STDs by the CDC) of these viruses[7]. The treatment regimen for hepatitis B currently includes Tenofovir and Entecavir, which both have hepatotoxicity as a potential side effect and thus, treatment of Hepatitis B could be limited. This further exemplifies why healthcare providers need to be extremely meticulous in their initial/continued patient information intake regarding herbal medications.

Per the literature, it is known that HIV or immunosuppressed patients are more susceptible to drug induced liver injury due to depleted glutathione stores. In conclusion, we present a case of drug-induced hepatitis in an HIV patient due to herbal medications advocated to boost the immune system to treat HIV. We advocate that acute hepatitis in patients with HIV may be due to massive doses of herbal medication use, aside from the usual viral and drug induced hepatotoxicities. Close questioning of patients on OTC medications, and more specifically, herbal drug use, is paramount in the evaluation of patients with hepatitis, especially in the setting of immunosuppression.

REFERENCES

1 **Chen GC**, Ramanathan VS, Law D, Funchain P, Chen GC, French S, Shlopov B, Eysselein V, Chung D, Reicher S, Pham BV. Acute liver injury induced by weight-loss herbal supplements. *World J Hepatol* 2010; **2**: 410-415

2 **Herzenberg LA**, De Rosa SC, Dubs JG, Roederer M, Anderson MT, Ela SW, Deresinski SC, Herzenberg LA. Glutathione deficiency is associated with impaired survival in HIV disease. *Proc Natl Acad Sci USA* 1997; **94**: 1967-1972

3 The Merck Index. 11th ed. Whitehouse Station, NJ: Merck and Co Inc., 1989: 4369

4 **Lee WM**, Hynan LS, Rossaro L, Fontana RJ, Stravitz RT, Larson AM, Davern TJ, Murray NG, McCashland T, Reisch JS, Robuck PR. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology* 2009; **137**: 856-864, 864.e1

5 **Chandrasekara A**, Shahidi F. Inhibitory activities of soluble and bound millet seed phenolics on free radicals and reactive oxygen species. *J Agric Food Chem* 2011; **59**: 428-436

6 Center for Disease Control (CDC). Available from: URL: http://www.cdc.gov/hiv/resources/factsheets/coinfection.htm

7 **Konopnicki D**, Mocroft A, de Wit S, Antunes F, Ledergerber B, Katlama C, Zilmer K, Vella S, Kirk O, Lundgren JD. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS* 2005; **19**: 593-601

S- Editor Jia F **L- Editor** A **E- Editor** Zheng XM

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
doi:10.4254/wjh.v4.i8.252

World J Hepatol 2012 August 27; 4(8): 252-255
ISSN 1948-5182 (online)

CASE REPORT

A middle-aged lady with a pyogenic liver abscess caused by *Clostridium perfringens*

Siu-Tong Law, Ming Kai Lee

Siu-Tong Law, Ming Kai Lee, Division of Gastroenterology and Hepatology, Department of Medicine and Geriatrics, Tuen Mun Hospital, Tuen Mun, Hong Kong, China
Author contributions: Law ST and Lee MK were responsible for the patient care; Law ST was also responsible for the conception and writing of the manuscript; all authors read and approved the final manuscript.
Correspondence to: Siu-Tong Law, MBBS, FHKCP, FHKAM, Division of Gastroenterology and Hepatology, Department of Medicine and Geriatrics, Tuen Mun Hospital, Tuen Mun, Hong Kong, China. stl168@hotmail.com
Telephone: +852-24685386 Fax: +852-24685389
Received: March 26, 2011 Revised: August 6, 2012
Accepted: August 23, 2012
Published online: August 27, 2012

Abstract

The pyogenic liver abscess caused by *Clostridium perfringens* (*C. perfringens*) is a rare, but rapidly fatal infection. It is usually associated with malignancy and immunosuppression. We report the case of 50-year-old lady with the secondary liver metastases from rectal cancer presented with fever and epigastric pain. The identification of *Gram-positive bacilli* septicaemia, the presence of gas-forming liver abscess and massive intravascular hemolysis should lead to the suspicion of *C. perfringens* infection. Here we review twenty cases published since 1990 and their clinical features are discussed. The importance of "an aggressive treatment policy" with multidisciplinary team approach is emphasized.

Key words: Pyogenic liver abscess; *Clostridium perfringens*; Infected hepatic metastases; Liver abscess; Gram-positive bacilli septicaemia

Peer reviewer: Marcelo AF Ribeiro Jr, Professor, Department of Surgery, UNISA, Rua José de Jesus 66 apto 84C, São Paulo 05630090, Brazil

Law ST, Lee MK. A middle-aged lady with a pyogenic liver abscess caused by *Clostridium perfringens*. *World J Hepatol* 2012; 4(8): 252-255 Available from: URL: http://www.wjgnet.com/1948-5182/full/v4/i8/252.htm DOI: http://dx.doi.org/10.4254/wjh.v4.i8.252

INTRODUCTION

Pyogenic liver abscess caused by *Clostridium perfringens* (*C. perfringens*) is a rare, but rapidly fatal, infection. Massive haemolysis and gas-forming liver abscess are classical features of this infection, which may prompt early recognition and treatment. This report is of a patient with the secondary liver metastases from rectal cancer with *C. perfringens* liver abscess. We also review all the previously reported cases of *C. perfringens* associated liver abscess published in the English literature since 1990 and highlights that this condition is usually associated with malignancy and immunosuppression and should be treated "aggressively" with multidisciplinary team approach.

CASE REPORT

A 50-year-old lady was admitted with epigastric pain and fever in July 2005. She had rectal cancer with multiple liver secondary diagnosed in August 2004 and was managed conservatively. Concerning her present illness, she had acute epigastric pain poorly localized without associated gastrointestinal symptoms. Her temperature was 38.4 ℃, blood pressure 95/64 with pulse 126 bpm. The abdominal examination showed hepatomegly with liver span of 13 cm. Laboratory data were as follow: hemoglobin, 8.3 g/dL (normal, 11.6-15.5 g/dL); white blood cell count, 46.3/mm^3 (normal, 3.9-10.7/mm^3); platelet count, 481/mm^3 (normal, 152-358/mm^3), APTT 38.9 (normal, 24.5-37.6), reticulocyte count, 7% (normal, < 2%); sodium, 136 mmol/L (normal, 136-145 mmol/L); potassium, 3.5 mmol/L (normal, 3.5-5.1 mmol/L); urea,

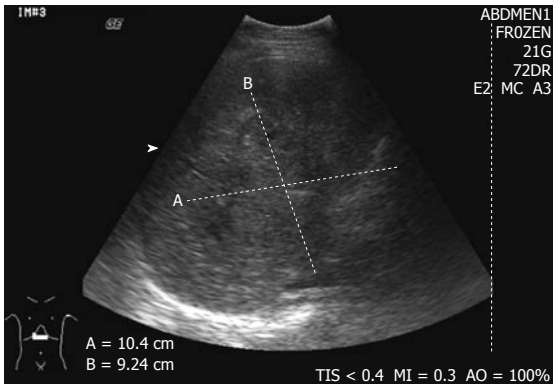


Figure 1 Ultrasound of liver showed mixed heterogeneous echogenicity lesions. Ill defined internal hyperechogenicity with "dirty shadow" appearance suspicious of gas content.

21.2 mmol/L (normal, 2.7-6.8 mmol/L); creatinine, 281 μmol/L (44-80 μmol/L); albumin, 14 g/L (normal, 35-50 g/L); globulin, 43 g/L (normal, no reference); total bilirubin, 153 μmol/L (normal, 5-20 μmol/L); alkaline phosphatase, 302 IU/L (normal, 43-141 IU/L); lactate dehydrogenase 1132 IU/L (normal, 211-370 IU/L). An urgent blood smear revealed the presence of *Gram-positive bacilli* and later identified as *C. perfringens*. She was treated with board-spectrum antibiotic (sulperazone 1 g Q12H and metronidazole 500 mg Q8H intravenously), vigorous fluid resuscitation with inotropic support (dopamine infusion of rate 20 mg/h intravenously) and blood cell transfusion. An urgent ultrasound of the abdomen showed extensive multiple echogenic foci with casting shadows were seen over the right lobe which was compatible with gas-containing space-occupancy lesion (Figure 1). The common bile duct and the gallbladder were normal without any filling defects. The computed tomography of the abdomen and pelvis showed bilobed liver abscesses located at right lobe and segment two/three in which the former (15 cm × 12 cm) had central cavitation and the latter (7 cm × 5 cm) had capsular rupture, resulting in loculated fluid and gas collection medial to the stomach (Figure 2). In addition, the left intrahepatic duct was dilated due to the compression of left lobe abscess. The right-lobe liver abscess was drained percutaneously by ultrasound guided and the left intrahepatic duct obstruction was relieved by transhepatic biliary drainage inserted percutaneously. Nevertheless, her clinical condition deteriorated with multi-organ failure, including acute respiratory distress syndrome and acute renal failure. Finally she was succumbed at seventh day of hospitalization.

DISCUSSION

The patient had typical clinical features of pyogenic liver abscess including fever, epigastric pain, and space-occupancy lesion in imaging and positive blood culture. However, the presence of massive intravascular hemolysis (anemia, reticulocytosis, high lactate dehydrogenase, disproportionate hyperbilirulinemia with relative normal common bile duct), gas-forming liver abscesses and identification of Gram-positive bacilli septicemia should lead to the suspicious of *C. perfringens* infection. The risk factor of our patient was advanced malignancy.

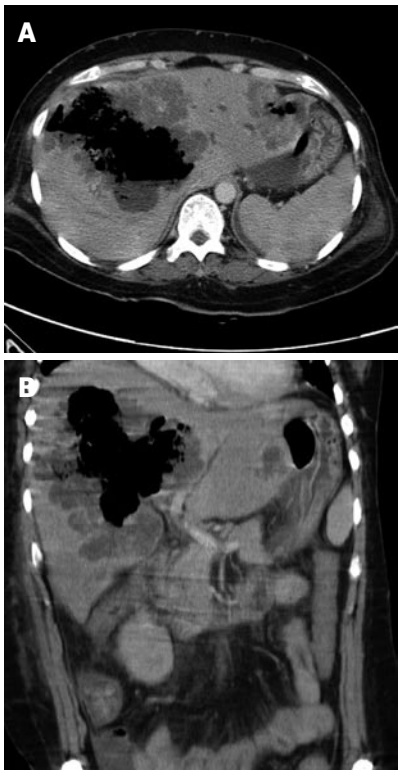


Figure 2 Axial (A) and sagittal (B) contrast multi-detector computerized tomography scan of abdomen. Rim-enhancing cystic lesions with internal gas content occupying both hepatic lobes with the largest occupying the right lobe.

C. perfringens is an ubiquitous, Gram-positive, spore-forming anaerobic bacillus (though, it is not absolute anaerobe as it can tolerate up to 3% O_2). It is normal inhabitant of the human bowel and genital tract. Like other clostridia, *C. perfringens* grows fast with doubling time of about 7 min and its virulence is related to its toxin production which contributes to the pathogenesis of the infection[1,2]. The main toxin is phospholipase C lecthinase (α toxin) which splits lecithin of red cell membrane into phosphocholine and diglyceride and thus damages the structural integrity of the cell membrane. This leads to spherocytosis and subsequent hemolysis. Occasionally, a blood smear can show ghost cells which appear empty because these cells have leaky membrane so that they can no longer retain hemoglobin. α-toxin is also key pathogenic factor in gas gangrene of clostridial soft tissue infection. Other virulence factors act primarily on the vascular endothelium, causing capillary leakage (β-, ε- and τ-toxin). Various risk factors for clostridium septicemia include elderly, poor controlled diabetic mellitus, cirrhosis and malignancy especially gastrointestinal and genitourinary malignancies[3]. In the case presented here, we postulate that the clostridium organisms grew within the devitalized tissue of rectal cancer and then migrated

Table 1 Cases of Clostridium perfringens liver abscesses published since 1990

No.	Author	Year	Age (yr)	Sex	Condition(s)	Hb (g/dL)	Bilirubin (mmol/L)	LDH (U/L)	Focus removed	Survival
1	Batge	1992	61	M	Pancreatic cancer	11.6	752.4	7600	Yes	Yes
2	Rogstad	1993	61	M	None		359.1	1344	No	No
3	Gutierrez	1995	74	M	None	13.1	70	1250	No	No
4	Jones	1996	66	F	Liver transplant	11.3	42.6		No	No
5	Eckel	2000	65	F	Cancer of common bile duct	11.2	78.7	350	Yes	Yes
6	Kreidl	2002	80	M	DM, ESRF		215.5		No	No
7	Pichon	2003	42	F	Alcoholic cirrhosis	10.2	210		No	Yes
8	Quigley	2003	73	M	Ischemic heart	14.2	71		No	No
9	Au	2005	65	M	DM, ESRF	6.2	160.7		No	No
10	Fondran	2005	63	M	Pancreatic cancer				Yes	Yes
11	Daly	2006	80	M	DM	8.7			No	No
12	Ohtani	2006	78	M	DM	10	23.9	51 382	No	No
13	Loran	2006	69	F	None	8.7	170		No	No
14	Agua	2009	74	M	Stroke		32.5		Yes	Yes
15	Merino	2009	83	F	None	12.2	335.2	2288	No	No
16	Meyns	2009	64	M	DM, myelodysplastic syndrome	7.2	141.4	980	No	No
17	Bradly	2010	52	M	Liver transplant		297.5		No	No
18	Ng	2010	61	F	DM	13.5	263	4054	Yes	Yes
19	Rajendran	2010	58	M	None	13.3			Yes	Yes
20	Law	2012	50	F	Rectal cancer	8.3	153	1529	No	No

M: Male; F: Female; ESRF: End stage renal failure; DM: Diabetic mellitus; Hb: Hemoglobin; LDH: Lactate dehydrogenese.

to liver *via* the portal venous system and then began to form local infection in liver parenchyma.

The clinical course of *C. perfringens* septicemia is usually rapidly deteriorated with high mortality rate ranging from 70% to 100%[4]. The treatment of choice is intravenously administrated high-dose penicillin (10-24 million units daily) and surgical debridement of all involved gangrenous tissue, which is thought to be crucial in preventing production of toxins[1]. *In vivo* studies, the combination of penicillin and clindamycin has better efficacy than penicillin alone in the suppression of toxin synthesis. When surgical debridement is difficult, hyperbaric oxygen therapy is worth considering as it can decrease toxin production rate and make the environment less anaerobic for the bacteria to grow because clostridia lack superoxide dismutase, making them incapable of surviving in the oxygen-rich environment created within a hyperoxic tissue[5,6]. The suggested regimen of hyperbaric oxygen is 2-3 atm oxygen for 60-120 min per session with 2-3 sessions per day for up to 6 d. In our case, imaging-guided liver abscess and biliary tract drainage was performed immediately once the diagnosis was made but the primary focus of infection still remained in the rectum. Thus the patient had dreadful outcome.

Since 1990, there are twenty cases of *C. perfringens* liver abscesses published in the English literature (including the current case) (Table 1)[7]. These cases had a median age of 65 years (range 42 to 83 years) and 13 (65%) were male. Five (25%) had the good past health[6,8-11]; four (20%) advanced malignancies, including two pancreatic[12,13], one hepatocellular[14] and one rectal cancer; six (30%) had diabetic mellitus[1,4,15-18], including two complicated with end-stage renal failure, one accompanied with myelodysplastic syndrome and the remaining three having diabetes as the only underlying disorder; three (15%) had cirrhosis[19-21], including two of them treated by liver transplantation and put on immunosuppressive therapy; one had stroke[22] and one had ischemic heart disease[23]. All cases except one (95%) presented with fever and twelve (60%) patients had abdominal pain and eight (40%) did not have localizing signs. One patient suddenly deteriorated and died at home before admission. By using χ^2 test, the abdominal pain was strongly associated with the rupture of the abscess ($\chi^2 = 7.18$, $P < 0.01$). All patients had features of massive intravascular hemolysis on admission, including hemoglobinemia, hemoglobinuria, and microspherocytes in the blood film, highly elevated bilirubin and lactate dehydrogenase. Except the case that died before admission, all cases had early identification of *C. perfringens* in the blood culture. For the morphology of the liver abscess, four (20%) cases were multiple diffuse microabscess; 14 (70%) cases were uniloculated (10 cases located at right and four cases at left lobe); one case was multiloculated at left lobe and one case was bilobed multiloculated. The mean hemoglobin and bilirubin level at presentation were 10.84 g/dL (SD = 2.4 g/dL) and 197.2 mmol/L (SD = 172.1 mmol/L) respectively. The measured hemoglobin level might be falsely high as it measured red cell bound and plasma free hemoglobin. The diagnosis of the liver abscess was made by follow: five cases at autopsy, 13 cases by computed tomography scan imaging and two cases by laparotomy. The indication of laparotomy for diagnosis was the acute abdomen. Only six cases survived (mortality rate of 30%) and five of them had the primary focus of infection removed. By using χ^2 test, their survivals were strongly associated with complete removal of infection focus ($\chi^2 = 11.61$, $P < 0.005$).The median hour of admission death was 11 h. Our patient died on the 7th day that was the longest one among the deaths. We believe this was the result of the

removal of the infected hepatic focus with the primary rectal focus staying behind.

In summary, *C. perfringens* septicemia is a rare but life-threatening disease which requires timely recognition to start an early and specific therapy to prevent mortality.

REFERENCES

1 **Ohtani S**, Watanabe N, Kawata M, Harada K, Himei M, Murakami K. Massive intravascular hemolysis in a patient infected by a Clostridium perfringens. *Acta Med Okayama* 2006; **60**: 357-360
2 **Hatheway CL**. Toxigenic clostridia. *Clin Microbiol Rev* 1990; **3**: 66-98
3 **Schröpfer E**, Rauthe S, Meyer T. Diagnosis and misdiagnosis of necrotizing soft tissue infections: three case reports. *Cases J* 2008; **1**: 252
4 **Ng H**, Lam SM, Shum HP, Yan WW. Clostridium perfringens liver abscess with massive haemolysis. *Hong Kong Med J* 2010; **16**: 310-312
5 **Wilkinson D**, Doolette D. Hyperbaric oxygen treatment and survival from necrotizing soft tissue infection. *Arch Surg* 2004; **139**: 1339-1345
6 **Rajendran G**, Bothma P, Brodbeck A. Intravascular haemolysis and septicaemia due to Clostridium perfringens liver abscess. *Anaesth Intensive Care* 2010; **38**: 942-945
7 **van Bunderen CC**, Bomers MK, Wesdorp E, Peerbooms P, Veenstra J. Clostridium perfringens septicaemia with massive intravascular haemolysis: a case report and review of the literature. *Neth J Med* 2010; **68**: 343-346
8 **Rogstad B**, Ritland S, Lunde S, Hagen AG. Clostridium perfringens septicemia with massive hemolysis. *Infection* 1993; **21**: 54-56
9 **Gutiérrez A**, Florencio R, Ezpeleta C, Cisterna R, Martínez M. Fatal intravascular hemolysis in a patient with Clostridium perfringens septicemia. *Clin Infect Dis* 1995; **20**: 1064-1065
10 **Loran MJ**, McErlean M, Wilner G. Massive hemolysis associated with Clostridium perfringens sepsis. *Am J Emerg Med* 2006; **24**: 881-883
11 **Merino A**, Pereira A, Castro P. Massive intravascular haemolysis during Clostridium perfrigens sepsis of hepatic origin. *Eur J Haematol* 2010; **84**: 278-279
12 **Bätge B**, Filejski W, Kurowski V, Klüter H, Djonlagic H. Clostridial sepsis with massive intravascular hemolysis: rapid diagnosis and successful treatment. *Intensive Care Med* 1992; **18**: 488-490
13 **Fondran J**, Williams GB. Liver metastasis presenting as pneumoperitoneum. *South Med J* 2005; **98**: 248-249
14 **Eckel F**, Lersch C, Huber W, Weiss W, Berger H, Schulte-Frohlinde E. Multimicrobial sepsis including Clostridium perfringens after chemoembolization of a single liver metastasis from common bile duct cancer. *Digestion* 2000; **62**: 208-212
15 **Kreidl KO**, Green GR, Wren SM. Intravascular hemolysis from a Clostridium perfringens liver abscess. *J Am Coll Surg* 2002; **194**: 387
16 **Au WY**, Lau LS. Massive haemolysis because of Clostridium perfringens [corrected] liver abscess in a patient on peritoneal dialysis. *Br J Haematol* 2005; **131**: 2
17 **Daly JJ**, Haeusler MN, Hogan CJ, Wood EM. Massive intravascular haemolysis with T-activation and disseminated intravascular coagulation due to clostridial sepsis. *Br J Haematol* 2006; **134**: 553
18 **Meyns E**, Vermeersch N, Ilsen B, Hoste W, Delooz H, Hubloue I. Spontaneous intrahepatic gas gangrene and fatal septic shock. *Acta Chir Belg* 2009; **109**: 400-404
19 **Jones TK**, O'Sullivan DA, Smilack JD. 66-year-old woman with fever and hemolysis. *Mayo Clin Proc* 1996; **71**: 1007-1010
20 **Pichon N**, François B, Pichon-Lefièvre F, Vincensini JF, Cessot F, Sautereau D. [Hepatic abscess from Clostridium perfringens septicemia]. *Gastroenterol Clin Biol* 2003; **27**: 237-238
21 **Bradly DP**, Collier M, Frankel J, Jakate S. Acute Necrotizing Cholangiohepatitis With Clostridium perfringens: A Rare Cause of Post-Transplantation Mortality. *Gastroenterol Hepatol* (N Y) 2010; **6**: 241-243
22 **Alarcón Del Agua I**, Flores Cortés M, Pareja Ciuró F, Puppo Moreno A, Jiménez Rodríguez R. [Spontaneous rupture of a Clostridium Perfringens liver abscess into the abdominal cavity]. *Cir Esp* 2009; **85**: 187-189
23 **Quigley M**, Joglekar VM, Keating J, Jagath S. Fatal Clostridium perfringens infection of a liver cyst. *J Infect* 2003; **47**: 248-250

S- Editor Jia F **L- Editor** A **E- Editor** Zheng XM

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
www.wjgnet.com

World J Hepatol 2012 August 27; 4(8): I
ISSN 1948-5182 (online)

Acknowledgments to reviewers of *World Journal of Hepatology*

We acknowledge our sincere thanks to our reviewers. Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of our World Series Journals. Both the editors of the journals and authors of the manuscripts submitted to the journals are grateful to the following reviewers for reviewing the articles (either published or rejected) over the past period of time.

Yasemin Hatice Balaban, Professor, Hacettepe University, Birlik Mahallesi 415. Sokak Oyak Sitesi No.45/3 Cankaya, Ankara 06570, Turkey

Ioannis Diamantis, Professor, University Of Athens, Athens 15238, Greece

Joan Genescà, Professor, Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Passeig Vall d'Hebron 119, Barcelona 08035, Spain

Dr. Nattiya Hirankarn, Department of Microbiology, Faculty of Medicine, Chulalongkorn University, Rama 4 road, Bangkok 10330, Thailand

Olivier Lesur, Professor, Department of Medicine, University of Sherbrooke, 3001 12e Ave N, Sherbrooke J1H 5N4, Quebec, Canada

Eiji Miyoshi, Professor, Osaka University Graduate School of Medicine, Suita 565-0871, Japan

Dr. Jordi Muntané, Liver Research Unit, Reina Sofia University Hospital, Córdoba 14004, Spain

Dr. María Angeles Pajares, PhD, Department of Metabolismo y Señalización Celular, Instituto de Investigaciones Biomedicas A. Sols (CSIC-UAM), Arturo Duperier 4, Madrid 28029, Spain

Ali Sazci, Professor, Department of Medical Biology and Genetics, Faculty of Medicine, University of Kocaeli, Kocaeli 41380, Turkey

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
www.wjgnet.com

World J Hepatol 2012 August 27; 4(8): I
ISSN 1948-5182 (online)

Events Calendar 2012

January 18, 2012
AHPBA Sponsored Consensus Conference on the Multidisciplinary Treatment of Colorectal Cancer Liver Metastases
San Francisco, CA, United States

January 20-21, 2012
AGA Clinical Congress of Gastroenterology and Hepatology: Practice, Evidence and Quality in 2012
Miami, FL, United States

January 27-28, 2012
28th Annual Meeting of the German Association for the Study of the Liver
Hamburg, Germany

January 30-31, 2012
5th International Conference on the Management of Patients with Viral Hepatitis
Paris, France

February 8-10, 2012
Stockholm Liver Week 2012
Stockholm, Sweden

February 16-19, 2012
22nd Conference of the Asian Pacific Association for the Study of the Liver
Taipei, Taiwan, China

March 16 -17, 2012
Hepatitis Single Topic Conference
Atlanta, GA, United States

March 16-17, 2012
ESGE - Workshop on Advanced Endoscopy with Live Demonstrations
Vienna, Austria

March 31-April 1, 2012
27th Annual New Treatments in Chronic Liver Disease
San Diego, CA, United States

April 18-22, 2012
The International Liver Congress by EASL
Barcelona, Spain

April 27-28, 2012
The European Society for Paediatric Gastroenterology, Hepatology and Nutrition
Stockholm, Sweden

May 16-19, 2012
International Liver Transplant Society 18th Annual International Congress 2012
San Francisco, CA, United States

May 19-22, 2012
Digestive Disease Week 2012
San Diego, CA, United States

June 22-23, 2012
EASL Monothematic Conference: Vascular Liver Diseases
Tallin, Estonia

July 1-5, 2012
10th World Congress of the International Hepato-Pancreato-Biliary Association 2012
Paris, France

September 5-8, 2012
International Congress of Pediatric Hepatology, Gastroenterology and Nutrition
Sharm El-Sheikh, Egypt

September 7-9, 2012
Viral Hepatitis Congress 2012
Macclesfield, United Kingdom

September 7-9, 2012
The Viral Hepatitis Congress
Frankfurt, Germany

September 14-16, 2012
The International Liver Cancer Association's 6th Annual Conference
Berlin, Germany

September 20-22, 2012
Prague Hepatology Meeting 2012
Prague, Czech Republic

September 20-22, 2012
1st World Congress on Controversies in the Management of Viral Hepatitis
Prague, Czech Republic

October 18-20, 2012
2nd World Congress on Controversies in the Management of Viral Hepatitis
Berlin, Germany

November 9-13, 2012
AASLD - The Liver Meeting 2012
Boston, MA, United States

November 9-13, 2012
The Liver Meeting - 63rd Annual Meeting and Postgraduate Course of the American Association for the Study of Liver Diseases
Boston, MA, United States

November 14-18, 2012
4th World Congress of Pediatric Gastroenterology, Hepatology and Nutrition
Taipei, Taiwan, China

December 26-28, 2012
International Conference on Gastroenterology, Hepatology and Nutrition
Bangkok, Thailand

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
www.wjgnet.com

World J Hepatol 2012 August 27; 4(8): I-V
ISSN 1948-5182 (online)

GENERAL INFORMATION

World Journal of Hepatology (*World J Hepatol, WJH*, online ISSN 1948-5182, DOI: 10.4254), is a monthly, open access (OA), peer-reviewed journal supported by an editorial board of 573 experts in hepatology from 46 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

ISSN

ISSN 1948-5182 (online)

Editor-in-chief

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: +86-10-85381892
Fax: +86-10-85381893
E-mail: wjh@wjgnet.com
http://www.wjgnet.com

Indexed and abstracted in
PubMed Central, PubMed, Digital Object Identifier, and Directory of OA Journals.

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 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/esps/. 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: +86-10-85381892. 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 less than 256 words) and structured abstracts (no less than 480). The specific requirements for structured abstracts are as follows:

An informative, structured abstracts of no less 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 less than 140 words); RESULTS (no less 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 boldfaced 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 boldfaced 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 re-submitted online (http://www.wjgnet.com/1948-5182office/). The author should send the copyright transfer letter, responses to the reviewers, English language Grade B certificate (for non-native speakers of English) and final manuscript checklist to wjh@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

WJH is an international, peer-reviewed, OA, online journal. Articles published by this journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. Authors of accepted articles must pay a publication fee. Publication fee: 600 USD per article. Editorial, topic highlights, book reviews and letters to the editor are published free of charge.