ISSN 2218-4333 (online)

World Journal of *Clinical Oncology*

World J Clin Oncol 2012 December 10; 3(12): 150-158

Baishideng Publishing Group
www.wjgnet.com

WJCO World Journal of Clinical Oncology

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

Editorial Board

2010-2014

The *World Journal of Clinical Oncology* Editorial Board consists of 316 members, representing a team of worldwide experts in oncology. They are from 33 countries, including Australia (6), Belgium (2), Brazil (1), Canada (5), China (34), Egypt (2), Finland (1), France (4), Germany (14), Greece (7), Hungary (1), India (5), Iran (1), Israel (2), Italy (27), Japan (20), Malaysia (1), Mexico (1), Netherlands (6), New Zealand (1), Peru (1), Poland (1), Portugal (4), Saudi Arabia (1), Singapore (9), South Korea (7), Spain (7), Sweden (1), Switzerland (2), Thailand (2), Turkey (6), United Kingdom (11), and United States (123).

Klaus Mross, *Freiburg*
Lars Mueller, *Kiel*
Katharina Pachmann, *Jena*
Matthias Peiper, *Düsseldorf*
Gerd J Ridder, *Freiburg*
Harun M Said, *Wuerzburg*

Greece

Leonidas Duntas, *Athens*
Nicholas Pavlidis, *Ioannina*
Professor A Polyzos, *Athens*
Alexander D Rapidis, *Athens*
Evangelia Razis, *Athens*
Dimitrios Roukos, *Ioannina*
Kostas Syrigos, *Athens*

Hungary

Zsuzsa Schaff, *Budapest*

India

Tanya Das, *Kolkata*
G Arun Maiya, *Manipal*
Ravi Mehrotra, *Allahabad*
Sanjeeb K Sahoo, *Bhubaneswar*
Sarwat Sultana, *New Delhi*

Iran

Ali Kabir, *Tehran*

Israel

Avi Hefetz Khafif, *Tel-Aviv*
Doron Kopelman, *Caesarea*

Italy

Luca Arcaini, *Pavia*
Enrico Benzoni, *Tolmezzo*
Rossana Berardi, *Ancona*
Valentina Bollati, *Milan*
Emilio Bria, *Rome*
Guido Cavaletti, *Monza*
Paolo Chieffi, *Naples*
Marco Ciotti, *Rome*
Giuseppe G Di Lorenzo, *Naples*
Alfio Ferlito, *Udine*
Daris Ferrari, *Abbiategrasso*
Alessandro Franchi, *Florence*
Gennaro Galizia, *Naples*
Roberto Mazzanti, *Firenze*
Michele N Minuto, *Pisa*
Simone Mocellin, *Padova*
Nicola Normanno, *Naples*
Marco G Paggi, *Rome*
Domenico Rubello, *Rovigo*
Antonio Russo, *Palermo*
Daniele Santini, *Rome*
Bruna Scaggiante, Trieste
Riccardo Schiavina, *Bologna*
Enzo Spisni, *Bologna*
Bruno Vincenzi, *Rome*
Giovanni Vitale, *Cusano Milanino*

Japan

Hidefumi Aoyama, *Niigata*
Takaaki Arigami, *Kagoshima*
Narikazu Boku, *Shizuoka*
Kazuaki Chikamatsu, *Chuo*
Toru Hiyama, *Higashihiroshima*
Satoru Kakizaki, *Gunma*
Shuichi Kaneko, *Kanazawa*
Koji Kawakami, *Kyoto*
Hiroki Kuniyasu, *Kashihara*
Eiji Miyoshi, *Suita*
Toru Mukohara, *Kobe*
Atsushi Nakajima, *Tokyo*
Takahide Nakazawa, *Sagamihara*
Seishi Ogawa, *Tokyo*
Youngjin Park, *Chiba prefecture*
Naoya Sakamoto, *Tokyo*
Hidekazu Suzuki, *Tokyo*
Michiko Yamagata, *Shimotsuga-gun*
Hiroki Yamaue, *Wakayama*

Malaysia

Min-Tze Liong, *Penang*

Mexico

Rafael Moreno-Sanchez, *Mexico*

Netherlands

Jurgen J Futterer, *Nijmegen*
Bart M Gadella, *Utrecht*
Johannes A Langendijk, *Groningen*
IM Verdonck-de Leeuw, *Amsterdam*
J Voortman, *Amsterdam*

New Zealand

Joanna Skommer, *Auckland*

Peru

Henry L Gomez, *Lima*

Poland

Lukasz Wicherek, *Bydgoszcz*

Portugal

Antonio Araujo, *Porto*
Rui M Medeiros, *Porto*
Paula Ravasco, *Lisbon*
Rui Manuel Reis, *Braga*

Saudi Arabia

Shahab Uddin, *Riyadh*

Singapore

Wei Ning Chen, *Singapore*
John M Luk, *Singapore*
Shu Wang, *Singapore*
Celestial Yap, *Singapore*
Khay-Guan Yeoh, *Singapore*
George W Yip, *Singapore*
Yong Zhang, *Singapore*
Zhan Zhang, *Singapore*

South Korea

Ho-Seong Han, *Seoul*
Young-Seoub Hong, *Busan*
Ja Hyeon Ku, *Seoul*
Geon Kook Lee, *Goyang-si*
Jae Cheol Lee, *Seoul*
Woo Sung Moon, Jeonju
Hyun Ok Yang, *Gangeung*

Spain

Maurizio Bendandi, *Pamplona*
Joan Carles, *Barcelona*
Javier Cortés Castán, *Barcelona*
Jose M Cuezva, *Madrid*
Jesús Prieto, *Pamplona*

Sweden

Lalle Hammarstedt, *Stockholm*

Switzerland

A Lugli, *Basel*
Jacqueline Schoumans, *Lausanne*

Thailand

Suebwong Chuthapisith, *Bangkok*
Songsak Petmitr, *Bangkok*

Turkey

Nejat Dalay, *Istanbul*
Seher Demirer, *Ankara*
Zafer Özgür Pektaş, *Adana*
Alper Sevinc, *Gaziantep*
Engin Ulukaya, *Gorukle Bursa*
Isik G Yulug, *Ankara*

United Kingdom

Shahriar Behboudi, *London*
Alastair David Burt, *Newcastle*

Barbara Guinn, *Southampton*
Stephen Hiscox, *Cardiff*
Wen G Jiang, *Cardiff*
Youqiang Ke, *Liverpool*
Charles H Lawrie, *Oxford*
T H Marczylo, *Leicester*
Simon N Rogers, *Liverpool*
Abeezar I Sarela, *Leeds*
Alex Tonks, *Cardiff*

United States

Ali Syed Arbab, *Detroit*
Athanassios Argiris, *Pittsburgh*
Raffaele Baffa, *Gaithersburg*
Partha P Banerjee, *Washington*
Scott M Belcher, *Cincinnati*
Heather A Bruns, *Muncie*
Deliang Cao, *Springfield*
William E Carson III, *Columbus*
Disaya Chavalitdhamrong, *Bronx*
Jason Chen, *New York*
Oliver Chen, *Boston*
Jin Q Cheng, *Tampa*
Bruce D Cheson, *Washington*
Mei-Sze Chua, *Stanford*
Muzaffer Cicek, *Rochester*
Ezra EW Cohen, *Chicago*
Hengmi Cui, *Baltimore*
Q Ping Dou, *Detroit*
David W Eisele, *San Francisco*
Wafik S El-Deiry, *Hershey*
Mahmoud El-Tamer, *New York*
Armin Ernst, *Boston*
Zeev Estrov, *Houston*
Marwan Fakih, *Buffalo*
Michelle A Fanale, *Houston*
Xianjun Fang, *Richmond*
Benjamin L Franc, *Sacramento*
Giulia Fulci, *Boston*
David H Garfield, *Denver*
Antonio Giordano, *Philadelphia*
S Murty Goddu, *St. Louis*
Yun Gong, *Houston*
Lei Guo, *Jefferson*
Sanjay Gupta, *Cleveland*
Subrata Haldar, *Cleveland*
Sam M Hanash, *Seattle*
Randall E Harris, *Columbus*
Andrea A Hayes-Jordan, *Houston*
David W Hein, *Louisville*
Paul J Higgins, *Albany*
James R Howe, *Iowa*
Hedvig Hricak, *New York*
Chuanshu Huang, *Tuxedo*
Wendong Huang, *Duarte*
Naijie Jing, *Houston*
Masao Kaneki, *Charlestown*
Hagop Kantarjian, *Houston*
Maria C Katapodi, *Ann Arbor*
Mark R Kelley, *Indianapolis*
Venkateshwar G Keshamouni, *Ann Arbor*
Nikhil Ishwar Khushalani, *Buffalo*
Arianna L Kim, *New York*
K Sean Kimbro, *Atlanta*
Leonidas G Koniaris, *Miami*
Hasan Korkaya, *Ann Arbor*
Sunil Krishnan, *Houston*
Melanie H Kucherlapati, *Boston*
Paul C Kuo, *Maywood*
Andrew C Larson, *Chicago*
Felix Leung, *North Hills*
Ho-Sheng Lin, *Detroit*
Jennifer Lin, *Boston*
Shiaw-Yih Lin, *Houston*
Steven E Lipshultz, *Miami*
Bolin Liu, *Aurora*
Jeri A Logemann, *Evanston*
Bert Lum, *South San Francisco*
Jian-Hua Luo, *Pittsburgh*
Shyamala Maheswaran, *Charlestown*
David L McCormick, *Chicago*
Murielle Mimeault, *Omaha*
Monica Mita, *San Antonio*
Gerard E Mullin, *Baltimore*
Ravi Murthy, *Houston*
Jacques E Nör, *Ann Arbor*
James S Norris, *Charleston*
Scott Okuno, *Rochester*
Timothy Michael Pawlik, *Baltimore*
Joseph A Paydarfar, *Lebanon*
Jay J Pillai, *Baltimore*
Luis F Porrata, *Rochester*
Raj S Pruthi, *Chapel Hill*
Jianyu Rao, *Los Angeles*
Steven A Rosenzweig, *Charleston*
Eric Rowinsky, *Warren*
Jose Russo, *Philadelphia*
Stephen H Safe, *College Station*
Adnan Said, *Madison*
Stewart Sell, *Albany*
Shahrokh F Shariat, *New York*
Jing Shen, *New York*
Dong Moon Shin, *Atlanta*
Haval Shirwan, *Louisville*
Viji Shridhar, *Rochester*
Anurag Singh, *Buffalo*
Lawrence J Solin, *Philadelphia*
David R Spigel, *Nashville*
Brendan Curran Stack, *Little Rock*
Charles F Streckfus, *Houston*
Lu-Zhe Sun, *San Antonio*
Vladimir N Uversky, *Indianapolis*
Jean-Nicolas Vauthey, *Houston*
Hanlin L Wang, *Los Angeles*
Thomas D Wang, *Ann Arbor*
Dennis D Weisenburger, *Omaha*
Robert P Whitehead, *Las Vegas*
Juergen K Willmann, *Stanford*
Jason D Wright, *New York*
Q Jackie Wu, *Durham*
Shenhong Wu, *Stony Brook*
Hang Xiao, *Amherst*
Mingzhao Xing, *Baltimore*
Ronald Xiaorong Xu, *Columbus*
Kaiming Ye, *Fayetteville*
William Andrew Yeudall, *Richmond*
Dihua Yu, *Houston*
Bao-Zhu Yuan, *Morgantown*
Yawei Zhang, *New Haven*
Weixiong Zhong, *Madison*
Shufeng Zhou, *Tampa*
Yue Zou, *Johnson*

WJCO World Journal of Clinical Oncology

Contents

Monthly Volume 3 Number 12 December 10, 2012

NAME OF JOURNAL
World Journal of Clinical Oncology

ISSN
ISSN 2218-4333 (online)

LAUNCH DATE
November 10, 2010

FREQUENCY
Monthly

EDITING
Editorial Board of *World Journal of Clinical Oncology*
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: wjco@wjgnet.com
http://www.wjgnet.com

EDITOR-IN-CHIEF
Stuart K Calderwood, PhD, Associate Professor,
Director Molecular and Cellular Radiation Oncology, Department of Radiation Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, 99 Brookline Avenue, Boston, MA 02215, United States

EDITORIAL OFFICE
Jian-Xia Cheng, Director
Jin-Lei Wang, Vice Director
World Journal of Clinical Oncology
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: wjco@wjgnet.com
http://www.wjgnet.com

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: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
December 10, 2012

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2218-4333/g_info_20100722172206.htm

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/esps/
wjco@wjgnet.com
doi:10.5306/wjco.v3.i12.150

World J Clin Oncol 2012 December 10; 3(12): 150-154
ISSN 2218-4333 (online)

EDITORIAL

Multiple roles of angiotensin in colorectal cancer

Hiroki Kuniyasu

Hiroki Kuniyasu, Department of Molecular Pathology, Nara Medical University, 840 Shijo-cho, Kashihara 634-8521, Japan
Author contributions: Kuniyasu H contributed solely to this work.
Supported by Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science, Japan
Correspondence to: Hiroki Kuniyasu, MD, PhD, Professor, Chairman, Department of Molecular Pathology, Nara Medical University, 840 Shijo-cho, Kashihara 634-8521, Japan. cooninh@zb4.so-net.ne.jp
Telephone: +81-744-223051 Fax: +81-744-257308
Received: July 19, 2012 Revised: September 28, 2012
Accepted: November 17, 2012
Published online: December 10, 2012

Abstract

Colorectal cancer (CRC) cells express renin and chymase through which they can activate angiotensin. Renin expression is induced by hyperglycemic conditions. As angiotensinogen is produced in the liver, CRC cells that can activate angiotensin have an enhanced ability to metastasize to this organ. In human CRC cases, patients with diabetes have higher activities of rennin and angiotensin-Ⅱ in primary tumors, and on average, have a more progressed disease stage, especially with respect to liver metastasis. These patients exhibit a stronger association with Hemoglobin A1c levels and metastasis compared to patients without diabetes. In a combined diabetes/CRC liver metastasis mouse model, concurrent treatment with anti-angiotensin and hypoglycemic agents shows a synergic effect in terms of reduced liver metastasis and improved survival. The effect of anti-angiotensin treatment and blood sugar control as a baseline management for colon cancer patients with diabetes needs to be examined in clinical trials to establish whether it can prevent liver metastasis.

Key words: Angiotensin; Renin; Angiotensin Ⅱ receptor blocker; Diabetes; Liver metastasis

Peer reviewers: Antonio Araujo, MD, PhD, Medical Oncology Department, Portuguese Institute of Oncology – Porto Centre, R Dr Antonio Bernardino Almeida, 4200 Porto, Portugal; Bin Wu, MD, PhD, Professor, Chairman, Department of Gastroenterology, the Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou 510630, Guangdong Province, China

Kuniyasu H. Multiple roles of angiotensin in colorectal cancer. *World J Clin Oncol* 2012; 3(12): 150-154 Available from: URL: http://www.wjgnet.com/2218-4333/full/v3/i12/150.htm DOI: http://dx.doi.org/10.5306/wjco.v3.i12.150

INTRODUCTION

Various factors participate in colorectal cancer (CRC) progression, such as growth factors, angiogenic factors, and cytokines. Angiotensin is a well-known hypertensive hormone and also possesses protumoral functions. Angiotensin Ⅱ (A-Ⅱ), an active form of angiotensin, induces angiogenesis, cell growth, invasion *via* activation of the specific receptor, A-Ⅱ type 1 receptor (ATR1) to enhance development and progression of CRC. Some colorectal cancer cells possess the angiotensin-activating mechanism employing renin and chymase. Importantly, renin expression is upregulated by hyperglycemic condition. The data examining the importance of hyperglycemia/diabetes-induced angiotensin activation in the liver metastasis of colorectal cancer are described in this article.

PROTUMORAL EFFECT OF ANGIOTENSIN

Colorectal cancer is the fourth leading cause of cancer-related deaths in Japan, and cancer mortality continues to increase as the Western lifestyle gains popularity among the Japanese population[1]. Approximately 24% of CRC cases involving invasion beyond the submucosal layer showed liver metastasis during and/or after the operation to excise the tumor[2]. One-third of CRC patients died of liver metastasis[3], and only one-third or fewer CRC patients with liver metastasis respond to systemic chemotherapy, although even in these cases long-term survival

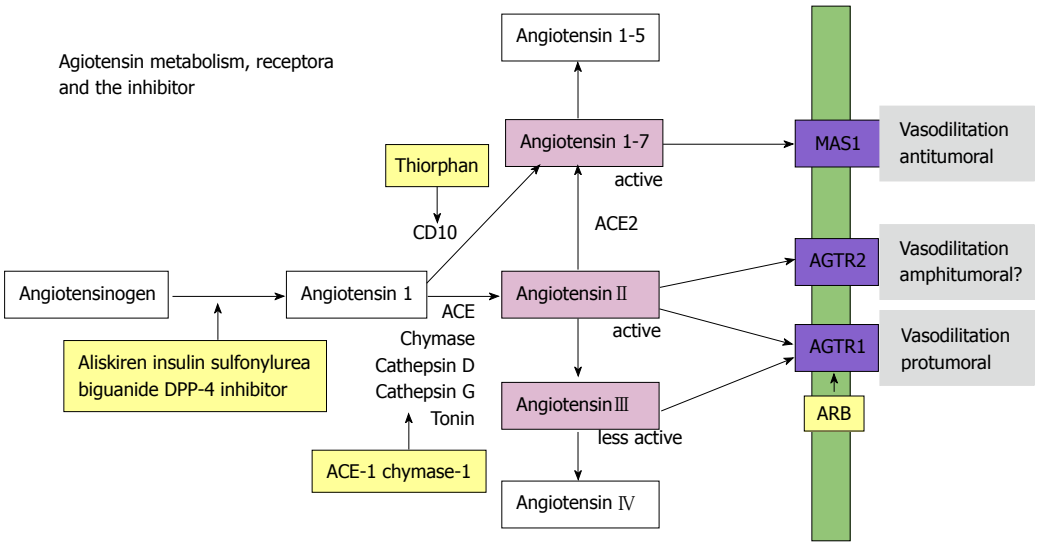

Figure 1 Aniotensinogen is activated to become a bioactive form, angiotensin Ⅱ by some enzymes, such as ACE. In angiotensin receptors (blue boxed), angiotensin Ⅱ type 1 receptor is pro-tumoral; however, angiotensin Ⅱ type 2 receptor is not definitive. Angiotensin 1-7, a degraded product of angiotensin Ⅱ activates MAS1 receptor to provide inhibitory effects. Substances marked with yellow boxes are possible inhibitors for angiotensin effects.

was rare[3]. The 5-year survival rate of CRC patients with liver metastasis is reported to be less than 20%[1]. The early detection and control of liver metastasis is therefore an important goal for the successful treatment of CRCs.

A-Ⅱ has multiple physiological effects mediated by the activation of the ATR1. These include vasoconstriction, inflammation, and proliferation in cardiovascular and neoplastic tissues[4]. ATR1 intracellular signaling pathways produce diverse effects, including activation of protein kinase C, angiopoietin 2, vascular endothelial growth factor (VEGF), VEGF receptors, fibroblast growth factor, platelet-derived growth factor, transforming growth factor-beta, epidermal growth factor, nitric oxide synthase, and metalloproteinase[4,5]. These properties enhance colon carcinogenesis and disease progression.

We have experimentally confirmed the protumor effect of angiotensin by studying the effects of A-Ⅱ on cell growth, invasion, and apoptosis in several CRC-derived cell lines[6]. A-Ⅱ enhances cell growth and *in vitro* invasion into type Ⅳ collagen and reduces apoptosis in a dose-dependent manner. Reduction in hepatic angiotensinogen (ATG) production by knockdown with cholesterol-conjugated antisense S-oligodeoxynucleotide (S-ODN) suppressed liver metastasis of HT29 cells in a nude mouse liver metastasis model. ATG-knockdown mice had fewer and smaller metastatic foci with a lower Ki-67 labeling index and reduced microvessel density, compared to the control mice. Knockdown of renin or chymase in HT29 cells also resulted in smaller and fewer metastatic foci in the liver compared to the control. Furthermore, examination of 121 CRC patients showed that the serum A-Ⅱ concentration is significantly associated with advanced disease stage, especially liver metastasis.

ANGIOTENSIN ACTIVATION IN CRC CELLS

As described above, the ability of angiotensin activation might be a prominent feature of cancer cell to obtain the powerful tool for progression. The mechanism of angiotensin activation in cancer is examined using colorectal cancer cell lines[6]. ATG is an inactive precursor of A-Ⅱ (Figure 1), and has no effect on cancer cells prior to conversion to A-Ⅱ. Effects of ATG on cell growth, invasion, and apoptosis were examined in HT29 cells. Interestingly, ATG enhanced cell growth, in vitro invasion, and anti-apoptotic survival in HT29 cells in a dose-dependent manner in a similar fashion to A-Ⅱ. This finding suggests that the HT29 cells have an endogenous angiotensin-activating mechanism.

We then examined the expression of angiotensin-associated genes in HT29 cells[6]. They express ATR1, but not ATG or angiotensin Ⅰ (A-Ⅰ)-converting enzyme (ACE). However, they express chymase, which possesses an ACE-like activity. Renin is also expressed in HT29 cells, and a renin inhibitor abrogates the production of both A-Ⅰ and A-Ⅱ. A chymase inhibitor suppresses the production of A-Ⅱ but not that of A-Ⅰ. In contrast, an ACE inhibitor does not affect the production of A-Ⅰ or A-Ⅱ in HT29 cells. Thus, A-Ⅱ is produced from ATG by renin and chymase in HT29 cells. Chymase, tonin, and cathepsin G all possess an ACE-like activity, which can be used as a substitute for ACE (Figure 1)[7]. Cathepsin D is responsible for producing A-Ⅰ from ATG in cardiac myocytes, fibroblasts, and vascular smooth muscle cells in place of renin[8]. However, the CRC cells in this study did not express cathepsin D. Chymase expression is associated with hypoxia or ischemia in the human left cardiac ventricle[9]; it is not associated with hyperglycemia in CRC cells[6].

MAS1

MAS1 is a receptor of an A-Ⅱ derivative produced by ACE 2-angiotensin 1-7 (A1-7), and has similar physiological effects to anti-A-Ⅱ, including vessel dilation and reduction

of blood pressure (Figure 1)[10]. We examined the role of MAS1 in CRC and in invasive ductal carcinoma (IDC) of the breast[11]. MAS1 was not detected by immunohistochemistry in either CRCs or the normal colon mucosa. In contrast, normal mammary lobules and ducts expressed MAS1 at high levels, although MAS1 expression was attenuated in all IDCs. Of particular note was the greatly reduced MAS1 expression in scirrhous-type IDCs compared to other types. The decrease in MAS1 expression was associated with lymph node metastasis but not T factor, grade, or the status of the estrogen or progesterone receptor. The decrease in MAS1 expression was inversely associated with human epidermal growth factor receptor 2 (HER2) expression. Using a mouse breast cancer cell line, BALB-MC, which expresses MAS1, cell growth and in vitro invasion were examined. A1-7 treatment inhibited growth and invasion of BALB-MC cells, which were abrogated by MAS1 knockdown. MAS1 intracellular signaling involves Akt phosphorylation, protein kinase C activation, and mitogen-activated protein kinase inhibition[12]. These findings suggest that MAS1 might act as an inhibitory regulator of both normal breast tissue and breast cancer.

CD10

CD10, also known as common acute lymphoblastic leukemia antigen (CALLA), is a characteristic marker of various subgroups of B-cell type acute lymphocytic leukemia[13,14]. It is a zinc-dependent membrane metalloendopeptidase (also referred to as neutral endopeptidase (EC 3.4.24.11), enkephalinase, or neprilysin)[14]. CD10 is expressed in CRC and is associated with CRC metastases, especially liver metastasis[2,15,16]. Met-enkephalin (MENK) is a high-affinity substrate of CD10[17,18]. It is produced by hepatocytes under conditions of cellular stress, such as hepatitis, bile stasis, and liver metastasis[19-21]. MENK inhibits tumor growth and the establishment of metastatic foci[22]. CD10-positive CRC cells degrade MENK and escape from MENK-induced tumor suppression[22]. CD10 possesses a weak affinity to A-Ⅰ[23]; however, CD10 shows A-Ⅰ-degrading activity but not the A-Ⅰ-converting activity. The degradation of A-Ⅰ produces A1-7, a MAS1 ligand. As discussed above, MAS1 is not expressed in CRCs. CD10-induced A1-7 does not affect CRC progression.

DIABETES AND THE RENIN/ANGIOTENSIN SYSTEM

Diabetes mellitus is a common problem in countries adopting the Western lifestyle. Several epidemiological studies have shown an association between type 2 diabetes and the risk of colorectal, pancreatic, breast, liver, gastric, and endometrial cancer[24]. The risk of malignancies is increased at earlier stages in cases of abnormalities in glucose metabolism, and there is a linear relationship between cancer risk and plasma insulin levels[24]. With regard to CRCs, a meta-analysis of 15 studies, involving a total of 2 593 935 participants, showed that diabetes is associated with an increased risk of CRC [relative risk, 1.30; 95% confidence interval (CI), 1.20-1.40]. Diabetes is also associated with CRC mortality (relative risk, 1.26; 95% CI, 1.05-1.50)[25]. High glycated hemoglobin (HbA1c) levels are also associated with an increased risk of CRC (odds ratio, 1.57; 95% CI, 0.94-2.60)[26]. Several studies have demonstrated that hyperinsulinemia, elevated levels of C-peptide, elevated body mass index, high levels of insulin growth factor-1, low levels of insulin growth factor binding protein-3, high leptin levels, and low adiponectin levels are involved in carcinogenesis[27]. Increased blood concentrations of insulin and insulin-like growth factor are particularly important in enhancing the risk of CRC[28]. However, a detailed understanding of how diabetes might increase the risk of CRC is still lacking.

We examined the expression of renin in HT29 and CT26 cells in association with changing glucose concentration. When the medium contained 100 mg/dL glucose, renin protein was detected in HT29 cells but not in CT26 cells. When the medium contained glucose at 200 mg/dL or more, the expression of renin increased with increasing glucose concentration in a dose-dependent manner in both cell lines. CT26 cells also expressed chymase but not ACE, in a similar manner to HT29 cells. These findings suggest then that the CRC cells activate angiotensin when exposed to high glucose concentrations.

In the hyperglycemic mice fed with a high-glucose diet, the size, number, Ki67 labeling index, and microvessel density of the liver metastatic foci were greater than those in the normoglycemic mice fed with the control diet. Clinical studies have suggested that a similar situation exists in patients. In the examination of 121 CRC patients, the tumor renin concentration correlated with HbA1c levels and the tumor A-Ⅱ concentration correlated with the tumor renin concentration. Moreover, high blood HbA1c levels are associated with a higher incidence of liver metastasis in diabetes cases but not non-diabetes cases. In cardiac fibroblasts, a high concentration of glucose significantly increases intracellular A-Ⅱ levels by increasing the intracellular levels of renin[29].

A-Ⅱ AND LIVER METASTASIS OF COLORECTAL CANCER

The A-Ⅱ precursor, ATG is mainly produced in hepatocytes[30]. We confirmed that CRC cells possessing angiotensin-activating ability establish liver metastasis because they can produce abundant A-Ⅱ from AGT in the liver[6]. To examine the prometastatic effect, CRC cells with angiotensin-activating ability were used in the mouse liver metastasis model. We suppressed AGT production in the mouse liver by using pro-AGT antisense S-ODN, which significantly suppressed the liver metastasis of CRC cells. Thus, CRC cells with angiotensin-activating ability are more likely to form liver metastasis. In CRC cases, A-Ⅱ is associated with renin concentration in primary tumors[6]. Thus, high levels of A-Ⅱ in primary CRC tissues, which indicates the potential to activate angiotensin in CRC cells, was associated with a high frequency of liver metastasis.

The A-Ⅱ concentration in primary CRC tissues may be a good marker for liver metastasis.

ANGIOTENSIN-TARGETING THERAPY FOR COLORECTAL CANCER

The renin/angiotensin-activating system is recognized as an important molecular target for CRC prevention and treatment. Several inhibitors of the renin/angiotensin-activating system suppress cancer development, cancer cell growth, angiogenesis, and metastasis[4,5,31-34]. Inhibitors of the renin-angiotensin system are widely used to treat hypertension. We have shown that some anti-angiotensin agents, inhibitors of renin and chymase, suppress liver metastasis of CRCs[6,35]. In addition, ACE inhibitors and/or A-Ⅱ receptor blocker (ARB) have been reported to improve disease prognosis or progression in pancreatic and urogenital cancer[36,37].

We have also examined the combined effect of anti-angiotensin treatment and hypoglycemic treatment[35]. In a streptozotocin-induced BALB/c mouse diabetes model fed a high-calorie diet, the blood sugar level increased and was associated with increasing size and number of CT26 cell liver metastases. In this diabetes mouse model, we examined the effect of concurrent hypoglycemic and anti-angiotensin treatments[35]. Insulin and gliclazide (sulfonylurea) were administered with or without a renin inhibitor (aliskiren) to the liver metastasis mouse model fed a high-calorie diet and treated with streptozotocin injection. Treatment with insulin and gliclazide resulted in lower blood sugar levels compared to that in the untreated mice. The mice treated with insulin or gliclazide showed a decrease in the number of metastatic foci and improved survival compared to the untreated mice. Concurrent treatment with anti-angiotensin using aliskiren or captopril ARB and hypoglycemic agents (insulin or gliclazide) resulted in lower serum A-Ⅱ concentration, fewer metastatic foci, and longer survival compared to the untreated mice or the mice treated with hypoglycemic agents alone. Combined treatment with anti-angiotensin and hypoglycemic agents showed a synergistic inhibitory effect on liver metastasis. The mice treated with the combination showed suppression of liver metastasis and improved survival, equal to that of the control mice.

Given that the association between hyperglycemia and liver metastasis in colon cancer is a result of renin upregulation, diabetes status is likely to be a risk factor for liver metastasis. Control of blood sugar could, therefore, be important in preventing liver metastasis in colon cancer patients. The use of anti-angiotensin treatment and blood sugar control as a baseline management for colon cancer patients with diabetes deserves to be examined in clinical trials in order to establish whether it helps in the prevention of liver metastasis (Figure 1).

CONCLUSION

As described above, the angiotensin activation is a pivotal feature of colorectal cancer for disease progression and liver metastasis. The angiotensin blockade and blood sugar control are hopeful tools for suppressing the liver metastasis of colorectal cancer. These treatments are provided commonly to patients of the hypertension and diabetes in an effective and safe manner. For CRC patients, especially, in their postoperative status, the angiotensin blockade and blood sugar control are relevant to prevent the liver metastasis in addition to the anti-cancer chemotherapy.

REFERENCES

1 Cancer Statistics in Japan, 2008. 2008 ed. Tokyo: National Cancer Center, 2008. Available from: URL: http: //ganjoho.jp/public/statistics/pub/statistics01.html
2 **Fujimoto Y**, Nakanishi Y, Sekine S, Yoshimura K, Akasu T, Moriya Y, Shimoda T. CD10 expression in colorectal carcinoma correlates with liver metastasis. *Dis Colon Rectum* 2005; **48**: 1883-1889
3 **Fong Y**, Kemeny N, Paty P, Blumgart LH, Cohen AM. Treatment of colorectal cancer: hepatic metastasis. *Semin Surg Oncol* 1996; **12**: 219-252
4 **Escobar E**, Rodríguez-Reyna TS, Arrieta O, Sotelo J. Angiotensin II, cell proliferation and angiogenesis regulator: biologic and therapeutic implications in cancer. *Curr Vasc Pharmacol* 2004; **2**: 385-399
5 **Wu XZ**. New strategy of antiangiogenic therapy for hepatocellular carcinoma. *Neoplasma* 2008; **55**: 472-481
6 **Shimomoto T**, Ohmori H, Luo Y, Chihara Y, Denda A, Sasahira T, Tatsumoto N, Fujii K, Kuniyasu H. Diabetes-associated angiotensin activation enhances liver metastasis of colon cancer. *Clin Exp Metastasis* 2012; **29**: 915-925
7 **Belova LA**. Angiotensin II-generating enzymes. *Biochemistry* (*Mosc*) 2000; **65**: 1337-1345
8 **Kumar R**, Singh VP, Baker KM. The intracellular renin-angiotensin system: implications in cardiovascular remodeling. *Curr Opin Nephrol Hypertens* 2008; **17**: 168-173
9 **Nishimura H**, Hoffmann S, Baltatu O, Sugimura K, Ganten D, Urata H. Angiotensin I converting enzyme and chymase in cardiovascular tissues. *Kidney Int Suppl* 1996; **55**: S18-S23
10 **Ferreira AJ**, Bader M, Santos RA. Therapeutic targeting of the angiotensin-converting enzyme 2/Angiotensin-(1-7)/Mas cascade in the renin-angiotensin system: a patent review. *Expert Opin Ther Pat* 2012; **22**: 567-574
11 **Kuniyasu H.** Establish of anti-liver metastasis therapy of colorectal cancer-targeting of angiotensin activation system. Proceeding of Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science, Japan, 2011; 24601: 20590349
12 **Iwai M**, Horiuchi M. Devil and angel in the renin-angiotensin system: ACE-angiotensin II-AT1 receptor axis vs. ACE2-angiotensin-(1-7)-Mas receptor axis. *Hypertens Res* 2009; **32**: 533-536
13 **Patey G**, De La Baume S, Schwartz JC, Gros C, Roques B, Fournie-Zaluski MC, Soroca-Lucas E. Selective protection of methionine enkephalin released from brain slices by enkephalinase inhibition. *Science* 1981; **212**: 1153-1155
14 **Shipp MA**, Vijayaraghavan J, Schmidt EV, Masteller EL, D'Adamio L, Hersh LB, Reinherz EL. Common acute lymphoblastic leukemia antigen (CALLA) is active neutral endopeptidase 24.11 ("enkephalinase"): direct evidence by cDNA transfection analysis. *Proc Natl Acad Sci USA* 1989; **86**: 297-301
15 **Yao T**, Takata M, Tustsumi S, Nishiyama K, Taguchi K, Nagai E, Tsuneyoshi M. Phenotypic expression of gastrointestinal differentiation markers in colorectal adenocarcinomas with liver metastasis. *Pathology* 2002; **34**: 556-560
16 **Ohji Y**, Yao T, Eguchi T, Yamada T, Hirahashi M, Iida M, Tsuneyoshi M. Evaluation of risk of liver metastasis in

colorectal adenocarcinoma based on the combination of risk factors including CD10 expression: multivariate analysis of clinicopathological and immunohistochemical factors. *Oncol Rep* 2007; **17**: 525-530
17 **Sumitomo M**, Shen R, Nanus DM. Involvement of neutral endopeptidase in neoplastic progression. *Biochim Biophys Acta* 2005; **1751**: 52-59
18 **Ogasawara M**, Murata J, Ayukawa K, Saimi I. Differential effect of intestinal neuropeptides on invasion and migration of colon carcinoma cells in vitro. *Cancer Lett* 1997; **116**: 111-116
19 **Boyella VD**, Nicastri AD, Bergasa NV. Human hepatic met-enkephalin and delta opioid receptor-1 immunoreactivities in viral and autoimmune hepatitis. *Ann Hepatol* 2008; **7**: 221-226
20 **Spivey JR**, Jorgensen RA, Gores GJ, Lindor KD. Methionine-enkephalin concentrations correlate with stage of disease but not pruritus in patients with primary biliary cirrhosis. *Am J Gastroenterol* 1994; **89**: 2028-2032
21 **Nicoll J**, Axiotis CA, Bergasa NV. The delta opioid receptor 1 is expressed by proliferating bile ductules in rats with cholestasis: implications for the study of liver regeneration and malignant transformation of biliary epithelium. *Med Hypotheses* 2005; **65**: 1099-1105
22 **Kuniyasu H**, Luo Y, Fujii K, Sasahira T, Moriwaka Y, Tatsumoto N, Sasaki T, Yamashita Y, Ohmori H. CD10 enhances metastasis of colorectal cancer by abrogating the anti-tumoural effect of methionine-enkephalin in the liver. *Gut* 2010; **59**: 348-356
23 **Skidgel RA**, Erdös EG. Angiotensin converting enzyme (ACE) and neprilysin hydrolyze neuropeptides: a brief history, the beginning and follow-ups to early studies. *Peptides* 2004; **25**: 521-525
24 **Nicolucci A**. Epidemiological aspects of neoplasms in diabetes. *Acta Diabetol* 2010; **47**: 87-95
25 **Larsson SC**, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst* 2005; **97**: 1679-1687
26 **Saydah SH**, Platz EA, Rifai N, Pollak MN, Brancati FL, Helzlsouer KJ. Association of markers of insulin and glucose control with subsequent colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev* 2003; **12**: 412-418
27 **Pais R**, Silaghi H, Silaghi AC, Rusu ML, Dumitrascu DL. Metabolic syndrome and risk of subsequent colorectal cancer. *World J Gastroenterol* 2009; **15**: 5141-5148
28 **Giovannucci E**. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. *Am J Clin Nutr* 2007; **86**: s836-s842
29 **Singh VP**, Baker KM, Kumar R. Activation of the intracellular renin-angiotensin system in cardiac fibroblasts by high glucose: role in extracellular matrix production. *Am J Physiol Heart Circ Physiol* 2008; **294**: H1675-H1684
30 **Dzau VJ**. Implications of local angiotensin production in cardiovascular physiology and pharmacology. *Am J Cardiol* 1987; **59**: 59A-65A
31 **Grossman E**, Messerli FH, Goldbourt U. Carcinogenicity of antihypertensive therapy. *Curr Hypertens Rep* 2002; **4**: 195-201
32 **Attoub S**, Gaben AM, Al-Salam S, Al Sultan MA, John A, Nicholls MG, Mester J, Petroianu G. Captopril as a potential inhibitor of lung tumor growth and metastasis. *Ann N Y Acad Sci* 2008; **1138**: 65-72
33 **Deshayes F**, Nahmias C. Angiotensin receptors: a new role in cancer? *Trends Endocrinol Metab* 2005; **16**: 293-299
34 **Fyhrquist F**, Saijonmaa O. Renin-angiotensin system revisited. *J Intern Med* 2008; **264**: 224-236
35 **Luo Y**, Ohmori H, Shimomoto T, Fujii K, Sasahira T, Chihara Y, Kuniyasu H. Anti-angiotensin and hypoglycemic treatments suppress liver metastasis of colon cancer cells. *Pathobiology* 2011; **78**: 285-290
36 **Nakai Y**, Isayama H, Ijichi H, Sasaki T, Sasahira N, Hirano K, Kogure H, Kawakubo K, Yagioka H, Yashima Y, Mizuno S, Yamamoto K, Arizumi T, Togawa O, Matsubara S, Tsujino T, Tateishi K, Tada M, Omata M, Koike K. Inhibition of renin-angiotensin system affects prognosis of advanced pancreatic cancer receiving gemcitabine. *Br J Cancer* 2010; **103**: 1644-1648
37 **Miyajima A**, Kikuchi E, Kosaka T, Oya M. Angiotensin II Type 1 Receptor Antagonist as an Angiogenic Inhibitor in Urogenital Cancer. *Rev Recent Clin Trials* 2009; **4**: 75-78

S- Editor Jiang L **L- Editor** A **E- Editor** Lu YJ

World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/esps/
wjco@wjgnet.com
doi:10.5306/wjco.v3.i12.155

World J Clin Oncol 2012 December 10; 3(12): 155-158
ISSN 2218-4333 (online)

CASE REPORT

Ganglioneuroblastoma arising within a retroperitoneal mature cystic teratoma

Satoshi Hayama, Makoto Ohmi, Atsuya Yonemori, Takumi Yamabuki, Hitoshi Inomata, Kazuyoshi Nihei, Satoshi Hirano

Satoshi Hayama, Makoto Ohmi, Atsuya Yonemori, Takumi Yamabuki, Hitoshi Inomata, Kazuyoshi Nihei, Department of Surgery, Kushiro Red Cross Hospital, 21-14 Shineicyo, Kushiro, Hokkaido 085-8512, Japan
Satoshi Hirano, Department of Surgical Oncology, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido 085-8512, Japan
Author contributions: Hayama S, Ohmi M, Yonemori A, Yamabuki T, Inomata H, Nihei K and Hirano S designed the research; Hayama S and Ohmi M analyzed the data; Hayama S wrote the paper.
Correspondence to: Dr. Satoshi Hayama, MD, PhD, Department of Surgery, Kushiro Red Cross Hospital, 21-14 Shineicyo, Kushiro, Hokkaido 085-8512, Japan. s-hayama@par.odn.ne.jp
Telephone: +81-154-227171 Fax: +81-154-247880
Received: April 5, 2012 Revised: October 29, 2012
Accepted: November 11, 2012
Published online: December 10, 2012

Abstract

We discuss an extremely rare case of ganglioneuroblastoma arising within a retroperitoneal mature cystic teratoma. Radiological examinations showed a cystic tumor sandwiched between the pancreas and left kidney. Surgery was scheduled because the tumor seemed to have originated from the pancreas. En-block resection of the tumor with distal pancreatectomy, splenectomy, and left adrenalectomy was performed. In terms of macroscopic appearance, the tumor mainly consisted of a unilocular cystic mass, but the presence of a smaller, solid mass was also noted within the tumor. Histopathologic examination confirmed that the cystic mass was consistent with a mature cystic teratoma of the retroperitoneum, and in addition, a ganglioneuroblastoma was evident in the solid component. Histopathologically, the ganglioneuroblastomatous area was intimately associated with dermoid tissue of the mature cystic teratoma, thus this case was diagnosed to be a mature cystic teratoma with malignant transformation. To best of our knowledge, this is the first reported case of ganglioneuroblastoma arising in a mature cystic teratoma.

Key words: Ganglioneuroblastoma; Malignant transformation; Mature cystic teratoma; Retroperitoneum; Surgical treatment

Peer reviewer: Piura Benjamin, Ben Gurion University Negev, Gynaecology Oncology Unit, Department of obstetrics and Gynaecology, Soroka Medical Centre, POB 151, IL-84101 Beer Sheva, Israel

Hayama S, Ohmi M, Yonemori A, Yamabuki T, Inomata H, Nihei K, Hirano S. Ganglioneuroblastoma arising within a retroperitoneal mature cystic teratoma. *World J Clin Oncol* 2012; 3(12): 155-158 Available from: URL: http://www.wjgnet.com/2218-4333/full/v3/i12/155.htm DOI: http://dx.doi.org/10.5306/wjco.v3.i12.155

INTRODUCTION

Malignant transformation of mature cystic teratoma (MCT) is a rare complication occurring in approximately 1%-3% of patients with MCT[1]. Although any of the constituent tissues of a teratoma has the potential to undergo malignant transformation, squamous cell carcinoma is the most commonly associated malignancy[1]. Other reported malignancies arising in MCT include carcinoid tumor, adenocarcinoma, basal cell carcinoma, adenosquamous carcinoma, thyroid carcinoma, sebaceous carcinoma, malignant melanoma, sarcoma, and neuroectodermal tumor[1]. Ganglioneuroblastoma (GNB) is a primary malignant tumor with neuroendocrine dif-

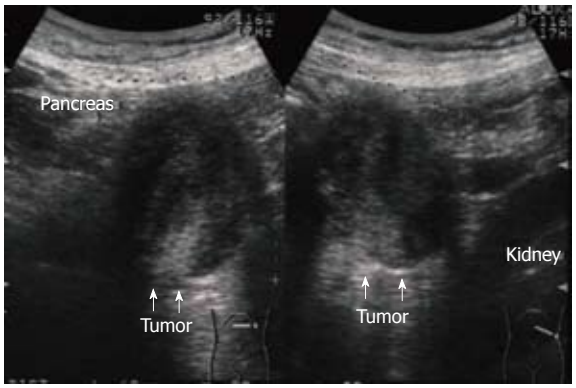

Figure 1 Abdominal ultrasonography showed a low-echoic mass sandwiched between the pancreas and left kidney, measuring 55 mm in its greatest diameter (arrows).

ferentiation, and is rarely seen in adults[2]. We treated a retroperitoneal MCT with ganglioneuroblastomatous transformation. To the best of our knowledge, this type of malignant transformation has never been reported in the international medical literature. We therefore present herein the clinicopathological findings of this extremely rare case.

CASE REPORT

A 55-year-old woman with a history of chronic hepatitis C infection presented to another hospital complaining of abdominal pain, general fatigue, and weight loss. Periumbilical tenderness was elicited on abdominal palpation, and laboratory data revealed liver dysfunction. Abdominal ultrasonography showed a low-echoic mass between the pancreas and left kidney measuring 55 mm in its greatest diameter (Figure 1). A primary pancreatic tumor was suspected and the patient was admitted to our hospital for further investigation. Abdominal computed tomography (CT) revealed the cystic tumor to have a thin wall with calcification, and to be accompanied by a solid component (Figure 2). The tumor seemed to have originated from the pancreatic body and to be in contact with the left adrenal gland. The liver dysfunction was thought to be the result of hepatitis C and improved with conservative treatment. The serum concentrations of the tumor markers carcinoembryonic antigen, carbohydrate antigen 19-9, s-pancreas-1 antigen, and Duke pancreatic monoclonal antigen type 2 were within normal ranges. Endoscopic retrograde cholangiopancreatography demonstrated a normal main pancreatic duct which did not communicate with the cystic tumor. Celiac arteriography did not show any tumor staining, and major vessels such as the portal vein, superior mesenteric vessels, and splenic vessels were not invaded or encased. We strongly suspected a pancreatic neoplasm such as mucinous cyst neoplasm and therefore scheduled the patient for surgery.

At surgery, after the gastrocolic omentum was dissected away from the transverse colon, the tumor was

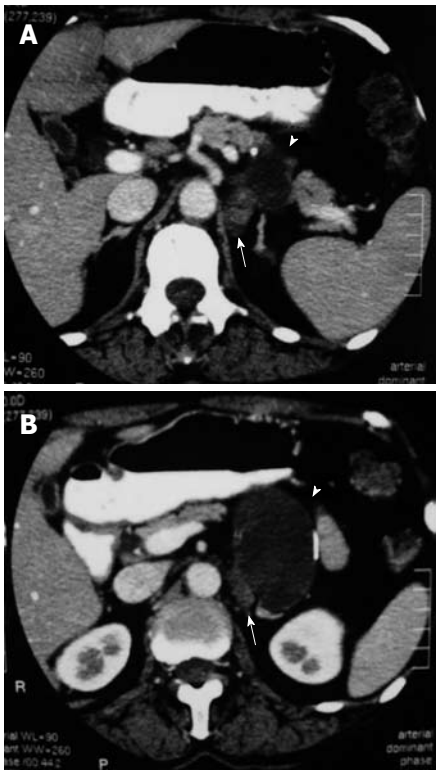

Figure 2 Abdominal computed tomography demonstrated a unilocular cystic tumor that appeared to be situated in the pancreas and contact with the left adrenal gland (arrowhead). The tumor had a thin wall with calcification, and a solid component was apparent (arrow).

palpated in the pancreatic body to tail. It seemed to be mainly situated in the posterior wall of the pancreas, and to have expanded into the retroperitoneal space, with involvement of the left adrenal gland. We therefore performed en-block R0 resection of the tumor with distal pancreatectomy, splenectomy, and left adrenalectomy.

Although intraoperative findings suggested that the pancreatic tumor involved the left adrenal gland, macroscopic examination of the surgical specimen revealed that the tumor was, in fact, separated from the pancreas by a fibrous tumor membrane. The tumor was a unilocular mass with an intact smooth capsule and measured 10 cm × 4 cm in diameter. Examination of the cut surface of the tumor indicated that this unilocular cyst was filled with homogenous, grayish, creamy fluid and contained hair and cheesy sebaceous material. On further examination, part of the tumor consisted of a solid mass measuring 3 cm × 2.5 cm in diameter, which was in contact with the left adrenal gland (Figure 3A and B).

Microscopically, sections from areas of the cyst wall contained squamous epithelium, hair follicle, and sebaceous glands. No immature elements were identified. These findings were consistent with a mature cystic teratoma. The solid component noted macroscopically, however, was histologically diagnosed as ganglioneuroblastoma. Positive immunohistochemical staining in this solid area for S-100 protein, neurofilament protein, and synaptophysin also supported this diagnosis. The area of ganglioneuroblastoma

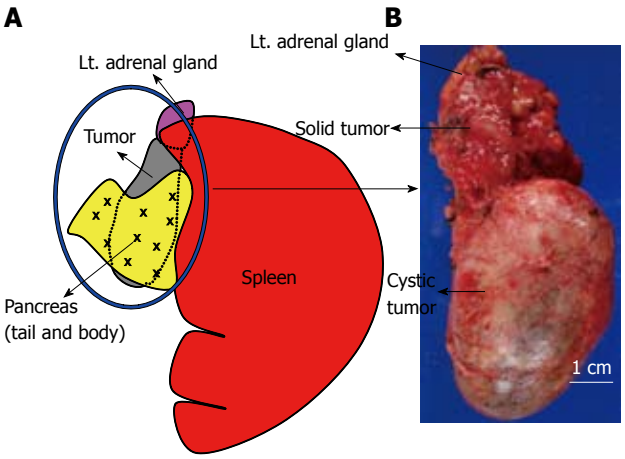

Figure 3 The schema shows the macroscopic appearance of the resected specimen. A: The cystic tumor (circled in blue) was separated from the pancreas by a fibrous tumor membrane; B: The tumor measured 10 cm × 4 cm in diameter and was filled with homogenous, grayish, creamy fluid. This tumor also had a solid component measuring 3 cm × 2.5 cm in diameter adjacent to the left adrenal gland.

was intimately associated with the mature cystic teratoma. Thus, the final diagnosis was ganglioneuroblastoma arising in retroperitoneal mature cystic teratoma. And en-block R0 resection of the tumor was obvious histopathologically (R0 resection indicates a microscopically margin-negative resection, in which no gross or microscopic tumor remains in the primary tumor bed[3]) (Figure 4).

The patient made an uneventful postoperative recovery and was discharged from hospital on the 19th postoperative day. She received neither adjuvant chemotherapy nor radiation therapy. Three years and ten months after the operation, she was in good health with no signs of recurrence.

DISCUSSION

Teratomas are uncommon neoplasms comprised of mixed dermal elements derived from the three germ cell layers. While the majority of teratomas are congenital and present in the ovaries of adolescent females and in the testes of young men, 1%-5% are found in extragonadal sites[4]. At week 4 of gestation, germ cells capable of differentiating to form tissue components of the three germ layers migrate down the fetal midline to reach the gonads. During this embryological migration, some of the cells can arrest and survive in an extragonadal location, mainly at mid-line sites[4], explaining why a few teratomas are found at these sites. The most frequent extragonadal site is the anterior mediastinum, followed by the retroperitoneum, sacrococcygeal, and intracranial regions[4]. Of the extragonadal teratomas, primary retroperitoneal teratomas are most commonly found in children and young adults[5], and the male to female ratio for this tumor is 1:2[4]. In many cases, retroperitoneal teratomas are metastases from the testes or ovaries, so it is important to distinguish true primary retroperitoneal teratomas from such metastatic lesions[5].

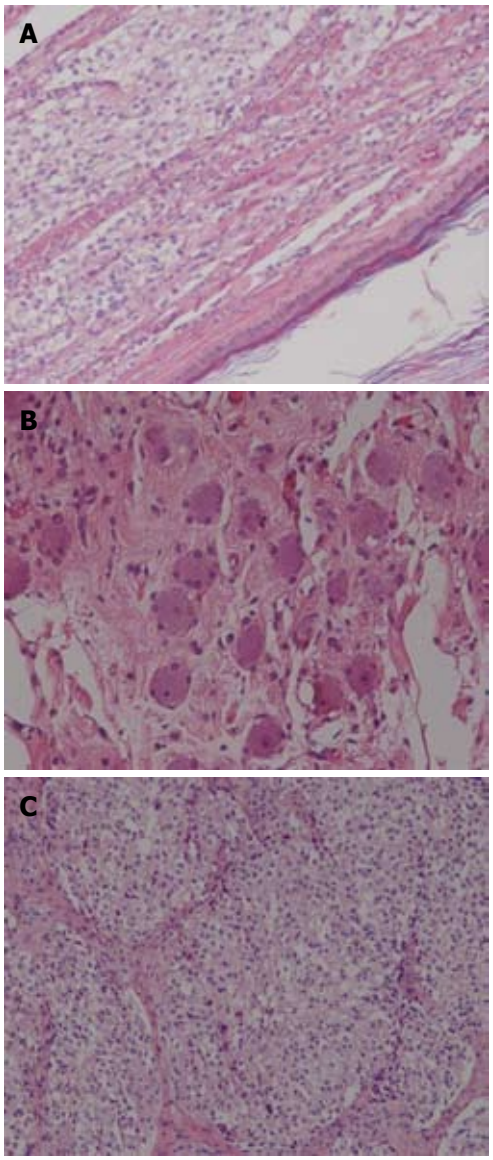

Figure 4 Histopathologic findings of the tumor. A: Benign squamous epithelium surrounding the cystic area (right lower part of figure) and ganglioneuroblastoma components (left upper part of figure) were adjacent and closely apposed to each other; B: Microscopic view of the mature, benign part of the ganglioneuroblastoma, showing ganglion cells and nerve fibers (hematoxylin and eosin, × 200); C: the malignant part of the ganglioneuroblastoma composed of neuroblasts (hematoxylin and eosin, × 200).

Teratomas are classified on the basis of their histopathologic findings and can be divided into two categories-mature and immature-which contain adult and embryonic type tissues, respectively[4]. Microscopically, MCTs are usually unilocular cysts containing tissue derived from all three germ cells, and may contain teeth, bone, and neural tissue[6]. The term teratoma with malignant transformation (TMT) refers to an existing MCT that gives rise to a malignant tumor; this is a rare event, occurring in approximately 1%-3% of all such lesions[1]. Primary retroperitoneal TMT is even rarer, with fewer than 20 cases reported in the literature[7]. Risk factors for malignancy in MCT include age over 45 years, tumor diameter greater than 10 cm, and rapid growth[6]. The most com-

mon malignancy has been reported as squamous cell carcinoma because many MCTs contain large amounts of squamous epithelium. However, although rare, other types of malignancies can occur within MCT: these include carcinoid tumor, adenocarcinoma, basal cell carcinoma, adenosquamous carcinoma, thyroid carcinoma, sebaceous carcinoma, malignant melanoma, sarcoma, and neuroectodermal tumor[1].

The preoperative diagnosis of retroperitoneal MCT may be aided by visualization of fluid, fat, soft tissue, and calcification in the tumor with both cystic and solid components on CT[7]. However, retroperitoneal MCT can be confused with various neoplasms as in the present case. Moreover, preoperative diagnosis of TMT is virtually impossible. Definitive diagnosis is made following surgical resection and histopathologic evaluation[5].

GNB is a primary malignant tumor of the sympathetic nervous system and generally considered a disease of early childhood that rarely occurs in adulthood[8]. GNB generally has a favorable prognosis, with no deaths from recurrence having been reported after complete resection. Nonetheless, this neoplasm is undoubtedly malignant, because most cases with distant metastasis die within 1 year[2]. This tumor, being of sympathetic-cell origin, can arise in various locations: in cervical, mediastinal, adrenal, and retroperitoneal locations in ascending order of frequency[8]. Similarly, GNB may arise when the sympathetic-cell component of MCT undergoes malignant transformation. In the present patient, the MCT most likely underwent malignant transformation toward the formation of GNB, although the pathogenic mechanism of TMT is not clearly understood. To the best of our knowledge, GNB arising within a MCT has never been reported. This unique case report suggests that sectioning of the entire MCT for histologic evaluation is indispensable to avoid missing a malignant tumor within the lesion. Because of the rarity of malignancies arising from MCT, there is no general agreement about the optimal treatment or prognostic factors of such tumors. In the present case, we assumed that, as for any GNB, complete excision would be associated with better survival.

In this case, the distinction between MCT with ganglioneuroblastomatous transformation versus collision tumors is of academic interest. Collision tumors occur when two different malignancies arise metachronously in the same organ. Although they are in contact at one point, for the most part the two lesions are separate from each other. In this reported case, however, the area of GNB was intimately associated with the MCT, which may rule out the diagnosis of collision tumor.

In conclusion, we reported an extremely rare case of ganglioneuroblastoma arising in a mature cystic teratoma. GNB without distant metastasis and for which radical resection is performed is reported to have a good prognosis. In the present case, we anticipated a favorable prognosis because complete resection was accomplished. However, because the nature of GNB arising within MCT remains unclear, further careful follow-up is warranted.

REFERENCES

1 **Park JH**, Whang SO, Song ES, Choi SJ, Lee WY. An ovarian mucinous cystadenocarcinoma arising from mature cystic teratoma with para-aortic lymph node metastasis: a case report. *J Gynecol Oncol* 2008; **19**: 275-278

2 **Yamanaka M**, Saitoh F, Saitoh H, Nisimura S, Sawada Y, Tsukui A, Kaimori M, Takahashi N. Primary retroperitoneal ganglioneuroblastoma in an adult. *Int J Urol* 2001; **8**: 130-132

3 **Hermanek P**, Wittekind C. Residual tumor (R) classification and prognosis. *Semin Surg Oncol* 1994; **10**: 12-20

4 **Scott AL**, Abbassi-Ghadi N, Archer CM, Swamy R, Gupta S. Neuroendocrine carcinoma arising within a retroperitoneal mature teratoma. *Ann R Coll Surg Engl* 2010; **92**: W5-W8

5 **Gatcombe HG**, Assikis V, Kooby D, Johnstone PA. Primary retroperitoneal teratomas: a review of the literature. *J Surg Oncol* 2004; **86**: 107-113

6 **Allam-Nandyala P**, Bui MM, Caracciolo JT, Hakam A. Squamous cell carcinoma and osteosarcoma arising from a dermoid cyst--a case report and review of literature. *Int J Clin Exp Pathol* 2010; **3**: 313-318

7 **Terado Y**, Kurata A, Ishida T, Imamura T, Sakamoto A. Adenocarcinoma of small intestinal type in retroperitoneal mature teratoma. *Pathol Int* 2010; **60**: 701-705

8 **Peycru T,** Guiramand J, Tardat E, Savoie PH, Avaro JP, Balandraud P. Nodular ganglioneuroblastoma in adults. *Can J Surg* 2009; **52**: E111-E113

S- Editor Gou SX **L- Editor** A **E- Editor** Lu YJ

World Journal of Clinical Oncology

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

World J Clin Oncol 2012 December 10; 3(12): I
ISSN 2218-4333 (online)

Acknowledgments to reviewers of *World Journal of Clinical Oncology*

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.

Noriko Nakajima, MD, PhD, Associate Professor, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Nihon University School of Medicine, 1-8-13 Kanda-surugadai Chiyoda-ku, Tokyo 101-8309, Japan

Kemik O, Department of General Surgery, Yuzuncu Yıl University Medical Faculty, Van 6500, Turkey

Choi SR, Department of Internal Medicine, Dong-A University College of Medicine, 3-1, Dongdaesin-dong, Seo-gu, Busan, 602-715, South Korea

WJCO World Journal of Clinical Oncology

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

World J Clin Oncol 2012 December 10; 3(12): I
ISSN 2218-4333 (online)

Events Calendar 2012

January 16-17, 2012
Biomarkers Summit Egypt
London, United Kingdom

January 25-26, 2012
Multi-Disciplinary Appoaches to Cancer Therapy
Dubai, United Arab Emirates

January 26-27, 2012
3rd National Conference: Renal and Bladder Cancer 2012
London, United Kingdom

January 30-31, 2012
2nd Annual Clinical Trials in Oncology
Rome, Italy

February 2-3, 2012
Stem Cells 2012 Conference and Exhibition
San Diego, CA, United States

February 6-8, 2012
Mahidol International Conference on Infections and Cancers 2012
Bangkok, Thailand

February 12-17, 2012
Keystone Symposia: Cancer and Metabolism
Alberta, Canada

February 22-25, 2012
Excellence in Oncology
Istanbul, Turkey

March 8-10, 2012
10th International Congress on Targeted Anticancer Therapies
Amsterdam, Netherlands

March 9-10, 2012
13th European Congress: Perspectives in Lung Cancer
Amsterdam, Netherlands

March 14-16, 2012
BTOC-11 Biological Therapy of Cancer
Munich, Germany

March 15-17, 2012
3rd Conference on Therapeutic Resistance in Cancer
Quebec, Canada

March 29-30, 2012
Modern methods of diagnosis and treatment of malignant tumors
Kiev, Ukraine

April 13-15, 2012
Asian Oncology Summit 2012
Singapore, Singapore

April 20-21, 2012
Diagnosis and treatment of advanced forms of prostate cancer, bladder cancer and kidney cancer
Kiev, Ukraine

April 20-22, 2012
The 9th Meeting of Asian Society for Neuro-Oncology
Taipei, Taiwan

April 26-28, 2012
3rd International Video Workshop on Radical Surgery in Gynaecological Oncology
Prague, Czech Republic

April 28, 2012
Issues in Pediatric Oncology
Kiev, Ukraine

May 5-6, 2012
Radiation Research Methods as A Diagnostic and Therapeutic Support in Oncology
Kiev, Ukraine

May 17-18, 2012
Eurasian forum on the management of patients with tumors of the gastrointestinal tract
Uman, Ukraine

June 16-17, 2012
Issues of Neurosurgery, vascular neurosurgery, neurooncology, spinal surgery and spinal cord
Kiev, Ukraine

July 7-10, 2012
22nd Biennial Congress of the European Association for Cancer Research
Barcelona, Spain

July 21-28, 2012
Cancer In Women
Hawaii, HI, United States

July 25-27, 2012
5th Latin American Conference on Lung Cancer
Rio de Janeiro, Brazil

August 27-30, 2012
UICC World Cancer Congress 2012
Québec, Canada

September 6-8, 2012
The 8th International Jordanian Oncology Society Conference
Amman, Jordan

September 27-28, 2012
Current issues of diagnosis and treatment of oncogynecology diseases
Ivano Frankivsk, Ukraine

September 27-29, 2012
European Conference of Oncology Pharmacy
Budapest, Hungary

October 5-8, 2012
44th Congress of the International Society of Paediatric Oncology
London, United Kingdom

October 13-16, 2012
14th Biennial Meeting of the International Gynecologic Cancer Society
Vancouver, Canada

October 19, 2012
Modern aspects of diagnosis and treatment of breast cancer
Kiev, Ukraine

October 23-26, 2012
Sydney International Breast Cancer Congress 2012
Sydney, Australia

October 27-28, 2012
Optimization methods for radiation diagnosis in oncology
Odessa, Ukraine

November 6-9, 2012
24th EORTC-NCI-AACR Symposium on "Molecular Targets and Cancer Therapeutics"
Dublin, Ireland

November 16-17, 2012
17th Annual Perspectives in Thoracic Oncology
New York, NY, United States

WJCO World Journal of Clinical Oncology

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

World J Clin Oncol 2012 December 10; 3(12): I-V
ISSN 2218-4333 (online)

GENERAL INFORMATION

World Journal of Clinical Oncology (*World J Clin Oncol*, *WJCO*, online ISSN 2218-4333, DOI: 10.5306) is a monthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 316 experts in oncology from 33 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. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

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 *WJCO* 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 *WJCO* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJCO* 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 aim of *WJCO* is to report rapidly new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of oncology. *WJCO* covers etiology, epidemiology, evidence-based medicine, informatics, diagnostic imaging, endoscopy, tumor recurrence and metastasis, tumor stem cells, radiotherapy, chemotherapy, interventional radiology, palliative therapy, clinical chemotherapy, biological therapy, minimally invasive therapy, physiotherapy, psycho-oncology, comprehensive therapy, oncology-related traditional medicine, integrated Chinese and Western medicine, and nursing. *WJCO* covers tumors in various organs/tissues, including the female reproductive system, bone and soft tissue, respiratory system, urinary system, endocrine system, skin, breast, nervous system, head and neck, digestive system, and hematologic and lymphatic system. The journal also publishes original articles and reviews that report the results of applied and basic research in fields related to oncology, such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

Columns

The columns in the issues of *WJCO* 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 Articles: To report innovative and original findings in oncology; (9) Brief Articles: To briefly report the novel and innovative findings in oncology; (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 *WJCO*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of oncology; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research oncology.

Name of journal

World Journal of Clinical Oncology

ISSN

ISSN 2218-4333 (online)

Editor-in-chief

Stuart K Calderwood, PhD, Associate Professor, Director
Molecular and Cellular Radiation Oncology, Department of Radiation Oncology, Beth Israel Deaconess Medical Center,

Harvard Medical School, 99 Brookline Avenue, Boston, MA 02215, United States

Editorial Office
World Journal of Clinical Oncology
Editorial Department: Room 903, Building D,
Ocean International Center,
No. 62 Dongsihuan Zhonglu,
Chaoyang District, Beijing 100025, China
E-mail: wjco@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-85381892
Fax: +86-10-85381893

Indexed and Abstracted in
PubMed Central, PubMed, Digital Object Identifier, and Directory of Open Access 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, *WJCO* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in 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 conform 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. Book 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 ICMJE 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/2218-4333/g_info_20100722172206.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to wjco@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: +86-10-59080039 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 *WJCO*, 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 and brief articles, 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/2218-4333/g_info_list.htm.

Illustrations

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

Tables

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

Notes in tables and illustrations

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

Acknowledgments

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

REFERENCES

Coding system

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

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

PMID and DOI

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

Style for journal references

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

Style for book references

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

Format

Journals

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

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

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

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

In press

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

Organization as author

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

Both personal authors and an organization as author

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

No author given

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

Volume with supplement

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

Issue with no volume

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

No volume or issue

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

Books

Personal author(s)

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

Chapter in a book (list all authors)

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

Author(s) and editor(s)

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

Conference proceedings

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

Conference paper

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

Electronic journal (list all authors)

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

Patent (list all authors)

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

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

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

Units

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

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/2218-4333/g_info_20100723153305.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/2218-4333/g_info_20100723140942.htm

Frontier: http://www.wjgnet.com/2218-4333/g_info_20100723141035.htm

Topic highlight: http://www.wjgnet.com/2218-4333/g_info_20100723141239.htm

Observation: http://www.wjgnet.com/2218-4333/g_info_20100723141532.htm

Guidelines for basic research: http://www.wjgnet.com/2218-4333/g_info_20100723142040.htm

Guidelines for clinical practice: http://www.wjgnet.com/2218-5836/g_info_20100723142248.htm

Review: http://www.wjgnet.com/2218-4333/g_info_20100723145519.htm

Original articles: http://www.wjgnet.com/2218-4333/g_info_20100723145856.htm

Brief articles: http://www.wjgnet.com/2218-4333/g_info_20100723150253.htm

Case report: http://www.wjgnet.com/2218-4333/g_info_20100723150420.htm

Letters to the editor: http://www.wjgnet.com/2218-4333/g_info_20100723150642.htm

Book reviews: http://www.wjgnet.com/2218-4333/g_info_20100723150839.htm

Guidelines: http://www.wjgnet.com/2218-4333/g_info_20100723150924.htm

SUBMISSION OF THE REVISED MANUSCRIPTS AFTER ACCEPTED

Authors must revise their manuscript carefully according to the revision policies of Baishideng Publishing Group Co., Limited. The revised version, along with the signed copyright transfer agreement, responses to the reviewers, and English language Grade B certificate (for non-native speakers of English), should be submitted to the online system *via* the link contained in the e-mail sent by the editor. If you have any questions about the revision, please send e-mail to esps@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/2218-4333/g_info_20100723153117.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/2218-4333/g_info_20100723152755.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

WJCO 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

WJCO is an international, peer-reviewed, Open-Access, 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. The related standards are as follows. Publication fee: 600 USD per article. Editorial, topic highlights, original articles, brief articles, book reviews and letters to the editor are published free of charge.