

World Journal of *Clinical Cases*

World J Clin Cases 2021 August 26; 9(24): 6964-7291



OPINION REVIEW

- 6964 Reconsideration of recurrence and metastasis in colorectal cancer
Wang R, Su Q, Yan ZP

MINIREVIEWS

- 6969 Multiple immune function impairments in diabetic patients and their effects on COVID-19
Lu ZH, Yu WL, Sun Y
- 6979 Discontinuation of antiviral therapy in chronic hepatitis B patients
Medas R, Liberal R, Macedo G

ORIGINAL ARTICLE**Case Control Study**

- 6987 Textural differences based on apparent diffusion coefficient maps for discriminating pT3 subclasses of rectal adenocarcinoma
Lu ZH, Xia KJ, Jiang H, Jiang JL, Wu M

Retrospective Cohort Study

- 6999 Cost-effective screening using a two-antibody panel for detecting mismatch repair deficiency in sporadic colorectal cancer
Kim JB, Kim YI, Yoon YS, Kim J, Park SY, Lee JL, Kim CW, Park IJ, Lim SB, Yu CS, Kim JC

Retrospective Study

- 7009 Novel model combining contrast-enhanced ultrasound with serology predicts hepatocellular carcinoma recurrence after hepatectomy
Tu HB, Chen LH, Huang YJ, Feng SY, Lin JL, Zeng YY
- 7022 Influence of volar margin of the lunate fossa fragment fixation on distal radius fracture outcomes: A retrospective series
Meng H, Yan JZ, Wang B, Ma ZB, Kang WB, Liu BG
- 7032 Case series of COVID-19 patients from the Qinghai-Tibetan Plateau Area in China
Li JJ, Zhang HQ, Li PJ, Xin ZL, Xi AQ, Zhuo-Ma, Ding YH, Yang ZP, Ma SQ
- 7043 Patients' awareness about their own breast cancer characteristics
Geng C, Lu GJ, Zhu J, Li YY
- 7053 Fracture risk assessment in children with benign bone lesions of long bones
Li HB, Ye WS, Shu Q

SYSTEMATIC REVIEWS

- 7062** Mothers' experiences of neonatal intensive care: A systematic review and implications for clinical practice
Wang LL, Ma JJ, Meng HH, Zhou J

META-ANALYSIS

- 7073** *Helicobacter pylori* infection and peptic ulcer disease in cirrhotic patients: An updated meta-analysis
Wei L, Ding HG

CASE REPORT

- 7085** Tuberous sclerosis complex-lymphangiomyomatosis involving several visceral organs: A case report
Chen HB, Xu XH, Yu CG, Wan MT, Feng CL, Zhao ZY, Mei DE, Chen JL
- 7092** Long-term survivor of metastatic squamous-cell head and neck carcinoma with occult primary after cetuximab-based chemotherapy: A case report
Große-Thie C, Maletzki C, Junghanss C, Schmidt K
- 7099** Genetic mutations associated with sensitivity to neoadjuvant chemotherapy in metastatic colon cancer: A case report and review of literature
Zhao L, Wang Q, Zhao SD, Zhou J, Jiang KW, Ye YJ, Wang S, Shen ZL
- 7110** Coexistence of cervical extramedullary plasmacytoma and squamous cell carcinoma: A case report
Zhang QY, Li TC, Lin J, He LL, Liu XY
- 7117** Reconstruction of the chest wall after resection of malignant peripheral nerve sheath tumor: A case report
Guo X, Wu WM, Wang L, Yang Y
- 7123** A rare occurrence of a hereditary Birt-Hogg-Dubé syndrome: A case report
Lu YR, Yuan Q, Liu J, Han X, Liu M, Liu QQ, Wang YG
- 7133** Late-onset Leigh syndrome without delayed development in China: A case report
Liang JM, Xin CJ, Wang GL, Wu XM
- 7139** New mechanism of partial duplication and deletion of chromosome 8: A case report
Jiang Y, Tang S, He F, Yuan JX, Zhang Z
- 7146** S-1 plus temozolomide as second-line treatment for neuroendocrine carcinoma of the breast: A case report
Wang X, Shi YF, Duan JH, Wang C, Tan HY
- 7154** Minimally invasive treatment of hepatic hemangioma by transcatheter arterial embolization combined with microwave ablation: A case report
Wang LZ, Wang KP, Mo JG, Wang GY, Jin C, Jiang H, Feng YF
- 7163** Progressive disfiguring facial masses with pupillary axis obstruction from Morbihan syndrome: A case report
Zhang L, Yan S, Pan L, Wu SF

- 7169** Idiopathic basal ganglia calcification associated with new *MYORG* mutation site: A case report
Fei BN, Su HZ, Yao XP, Ding J, Wang X
- 7175** Geleophysic dysplasia caused by a mutation in *FBNI*: A case report
Tao Y, Wei Q, Chen X, Nong GM
- 7181** Combined laparoscopic-endoscopic approach for gastric glomus tumor: A case report
Wang WH, Shen TT, Gao ZX, Zhang X, Zhai ZH, Li YL
- 7189** Aspirin-induced long-term tumor remission in hepatocellular carcinoma with adenomatous polyposis coli stop-gain mutation: A case report
Lin Q, Bai MJ, Wang HF, Wu XY, Huang MS, Li X
- 7196** Prenatal diagnosis of isolated lateral facial cleft by ultrasonography and three-dimensional printing: A case report
Song WL, Ma HO, Nan Y, Li YJ, Qi N, Zhang LY, Xu X, Wang YY
- 7205** Therapy-related myeloid leukemia during erlotinib treatment in a non-small cell lung cancer patient: A case report
Koo SM, Kim KU, Kim YK, Uh ST
- 7212** Pediatric schwannoma of the tongue: A case report and review of literature
Yun CB, Kim YM, Choi JS, Kim JW
- 7218** Status epilepticus as a complication after COVID-19 mRNA-1273 vaccine: A case report
Šin R, Štruncová D
- 7224** Successful outcome of retrograde pancreatojejunostomy for chronic pancreatitis and infected pancreatic cysts: A case report
Kimura K, Adachi E, Toyohara A, Omori S, Ezaki K, Ihara R, Higashi T, Ohgaki K, Ito S, Maehara SI, Nakamura T, Maehara Y
- 7231** Incidentally discovered asymptomatic splenic hamartoma misdiagnosed as an aneurysm: A case report
Cao XF, Yang LP, Fan SS, Wei Q, Lin XT, Zhang XY, Kong LQ
- 7237** Secondary peripheral T-cell lymphoma and acute myeloid leukemia after Burkitt lymphoma treatment: A case report
Huang L, Meng C, Liu D, Fu XJ
- 7245** Retroperitoneal bronchogenic cyst in suprarenal region treated by laparoscopic resection: A case report
Wu LD, Wen K, Cheng ZR, Alwalid O, Han P
- 7251** Coexistent vestibular schwannoma and meningioma in a patient without neurofibromatosis: A case report and review of literature
Zhao LY, Jiang YN, Wang YB, Bai Y, Sun Y, Li YQ
- 7261** Thoracoabdominal duplication with hematochezia as an onset symptom in a baby: A case report
Yang SB, Yang H, Zheng S, Chen G

- 7269 Dental management of a patient with Moebius syndrome: A case report
Chen B, Li LX, Zhou LL
- 7279 Epidural gas-containing pseudocyst leading to lumbar radiculopathy: A case report
Chen Y, Yu SD, Lu WZ, Ran JW, Yu KX
- 7285 Regression of intervertebral disc calcification combined with ossification of the posterior longitudinal ligament: A case report
Wang XD, Su XJ, Chen YK, Wang WG

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Aspirin-induced long-term tumor remission in hepatocellular carcinoma with adenomatous polyposis coli stop-gain mutation: A case report

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Abstract

BACKGROUND

Targeted therapy based on pathway analysis of hepatitis B-related hepatocellular carcinoma (HCC) may be a promising remedy.

CASE SUMMARY

The present case involved an advanced hepatocellular carcinoma (HCC) patient who did not receive local regional therapy and was intolerant to sorafenib. Total RNA extracted from the patient's tumor tissue was used to obtain the gene mutation profile. The c.3676A>T and c.4402A>T stop-gain mutations in adenomatous polyposis coli (APC) were the most prevalent (42.2% and 35.1%, respectively). MutationMapper analysis indicated that the functional domain of APC was lost in the two APC mutant genes. APC is a major suppressor of the Wnt signaling pathway. Thus, the Wnt pathway was exclusively activated due to APC dysfunction, as other elements of this pathway were not found to be mutated. Aspirin has been reported to suppress the Wnt pathway by inducing β -catenin phosphorylation through the activation of glycogen synthase kinase 3 beta *via* cyclooxygenase-2 pathway inhibition. Therefore, aspirin was administered to the patient, which achieved four years of disease control.

CONCLUSION

Exclusive mutations of APC of all the Wnt pathway elements could be a therapeutic target in HCC, with aspirin as an effective treatment option.

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Core Tip: Hepatocellular carcinoma (HCC) is a highly heterogeneous disease. Due to the differences in etiology and ethnicities, the driving genes in HCC are likely to be different globally. Adenomatous polyposis coli (APC) mutations are critical in a fraction of HCC patients, as APC mutations might trigger HCC by activating the Wnt pathway. The effects of this mutation could be consistently suppressed by aspirin. Thus, APC mutation-triggered HCC might be a new subgroup of chronic hepatitis B virus infection-related HCC. Wnt pathway inhibition could be an effective remedy for this subgroup of patients.

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INTRODUCTION

Some small molecular agents with multiple targets, including sorafenib, lenvatinib, and regorafenib, are reported to be effective against hepatocellular carcinoma (HCC) [1]. However, the efficacy of these agents is unpredictable. As the average overall survival of patients with advanced HCC is only approximately three months [2], primary resistance to first-line treatment may prevent the possibility of second-line remedies. Thus, precise therapy is needed for the treatment of advanced HCC.

In this era of precise therapy, treatments can be administered with maximum efficacy if the target is clearly identified. For the multi-targeted agents used for HCC, unsatisfactory safety profiles and limited improvement in overall survival have hindered their use in the treatment of advanced HCC. RNA sequencing can be used to identify the causative gene mutations in tumor tissues to provide more accurate targets for the treatment of HCC.

In this case of advanced HCC, we screened for mutations in an HCC patient using the Illumina HiSeq2000 platform and identified mutated adenomatous polyposis coli (APC) as the major driver gene. Aspirin was chosen as the targeted agent to treat this patient, which achieved disease control for at least four years.

CASE PRESENTATION

Chief complaints

Recurrent HCC with APC stop-gain mutation.

History of present illness

A Chinese male patient with chronic hepatitis B infection was admitted to the Cancer Center of Sun Yat-sen University for the treatment of HCC identified in the S6 segment of the liver by contrast computed tomography (CT) scan in June 2012. Radical resection was performed. Tumor recurrence was observed in March 2014. Transcatheter arterial chemoembolization (TACE) was performed followed by radiofrequency ablation with radical intent. However, the tumor recurred at the juncture of the S2 and S3 sections in September 2014. The tumor was resected. The tumor recurred in February 2015. A series of TACE procedures were performed as palliative local regional therapy from February 2015 to October 2016 at the Third Affiliated Hospital of Sun Yat-sen University. Sorafenib was administered after the first cycle of palliative TACE, but the treatment was suspended one month later due to grade III diarrhea. In that period, tumor progression was noted three times, which

made local regional therapy an inappropriate choice for disease control. Alteration of alpha-fetoprotein indicated the efficacy of each therapy (Figure 1A).

History of past illness

Untreated chronic hepatitis B.

Personal and family history

None.

Physical examination

Normal.

Laboratory examinations

RNA sequence-based precise therapy was also considered. RNA sequencing was conducted on recurrent tumor tissue from a needle core biopsy in April 2016 to identify the gene mutation(s). Sequencing revealed that APC mutations are the major driver mutations. Stop-gain c.3676A>T and c.4402A>T APC mutations were the most prevalent (42.2% and 35.1%, respectively). ABL1 missense mutations, TP53 stop-gain, and TNFAIP3 missense mutations were less frequent (Table 1).

The amino acid sequences of APC mutations indicated a strongly truncated APC protein (Supplementary data). MutationMapper analysis indicated that the functional domain of APC was lost in both mutants in HCC tissue (Figure 1B).

Imaging examinations

Recurrent HCC was revealed by CT.

Gene mutations screen

Gene mutations were screened from HCC tissue samples from four patients and circulating tumor DNA samples from 41 HCC patients at The Third Affiliated Hospital of Sun Yat-sen University between February 2016 to January 2018 using the Illumina HiSeq2000 platform. Their gene mutation profiles were compared with those of the global HCC population from the Catalog of Somatic Mutations in Cancer (COSMIC) database. For patients with APC mutations, the amino acid sequences of APC mutations were evaluated using the Mutation Taster (<http://www.mutationtaster.org/>) program. Using amino acid sequences generated by Mutation Taster, MutationMapper[3] was used to analyze the functional defects of the APC mutants.

HCC gene mutation profile of hepatitis B-related HCC

The gene mutation profile of Chinese patients with HCC was different to that of the global HCC population from the COSMIC database. According to our RNA sequence analysis of tumor tissues ($n = 4$) and circulating tumor DNA samples ($n = 41$) from hepatitis B-related HCC patients, the most prevalent mutated genes were TP53, APOB, KMT2D, LRP1B, EGFR, ATM, CHD7, CTNBN1, ARID1A, TSC2, FAT4, HNF1A, PTPRB, and APC (Figure 2A). This profile differed from the COSMIC global data (Figure 2B). Among the top 20 most frequent mutation genes, APOB, EGFR, ATM, CHD7, PTPRB, APC, and GNAS mutations were much more frequent among Chinese patients with HCC. Thus, these mutations may be potential targets for precise therapy.

APC is a major suppressive regulator of the Wnt pathway[4]. In this pathway, APC and glycogen synthase kinase 3 beta (GSK3 β) combined with Wnt pathway key regulator β -catenin induces β -catenin phosphorylation and degradation to avoid Wnt pathway over-activation. The Wnt pathway can be activated by multiple causes in HCC, including mutations in Axin1, Axin2, and β -catenin[5]. However, mutations in APC and GSK3 β are rare[6]. In the present study, APC was the only mutated gene in the Wnt pathway, which was presumed to be the exclusive cause of Wnt pathway over-activation. Due to the potentially normal function of other elements of the Wnt pathway, decreased β -catenin phosphorylation was the only trigger for this pathway. Thus, acceleration of β -catenin phosphorylation might abrogate the Wnt pathway, implicating GSK3 β as a potential target.

FINAL DIAGNOSIS

Recurrent HCC with APC stop-gain mutation.

Table 1 Gene mutation analysis

Gene	Mutation type	Mutation ratio (%)	Nucleotide change	Amino acid change	Chromosome	Genbank transcript ID
<i>ABL1</i>	Missense	30.2	c.1363G>C	p.Asp455His	9	NM_005157
<i>APC</i>	Stop-gain	42.2	c.3676A>T	p.Lys1226X	5	NM_000038
<i>APC</i>	Stop-gain	35.1	c.4402A>T	p.Lys1468X	5	NM_000038
<i>TP53</i>	Stop-gain	27.7	c.193A>T	p.Arg65X	17	NM_000546
<i>TNFAIP3</i>	Missense	5.5	c.1787G>A	p.Arg596Gln	6	NM_001270507
Gene	Mutation type	Folds	Starting position	Ending position	Chromosome	Genbank transcript ID
<i>MDM4</i>	Amplification	1.9	204485510	204527248	1	N/A

TREATMENT

Aspirin is reported to be effective in inducing β -catenin phosphorylation by activating GSK3 β due to inhibition of the cyclooxygenase 2 (COX2) pathway[7]. As the COX2 pathway was assumed to act normally, high-dose aspirin (0.3 g/day) was chosen as a remedy from April 2016.

OUTCOME AND FOLLOW-UP

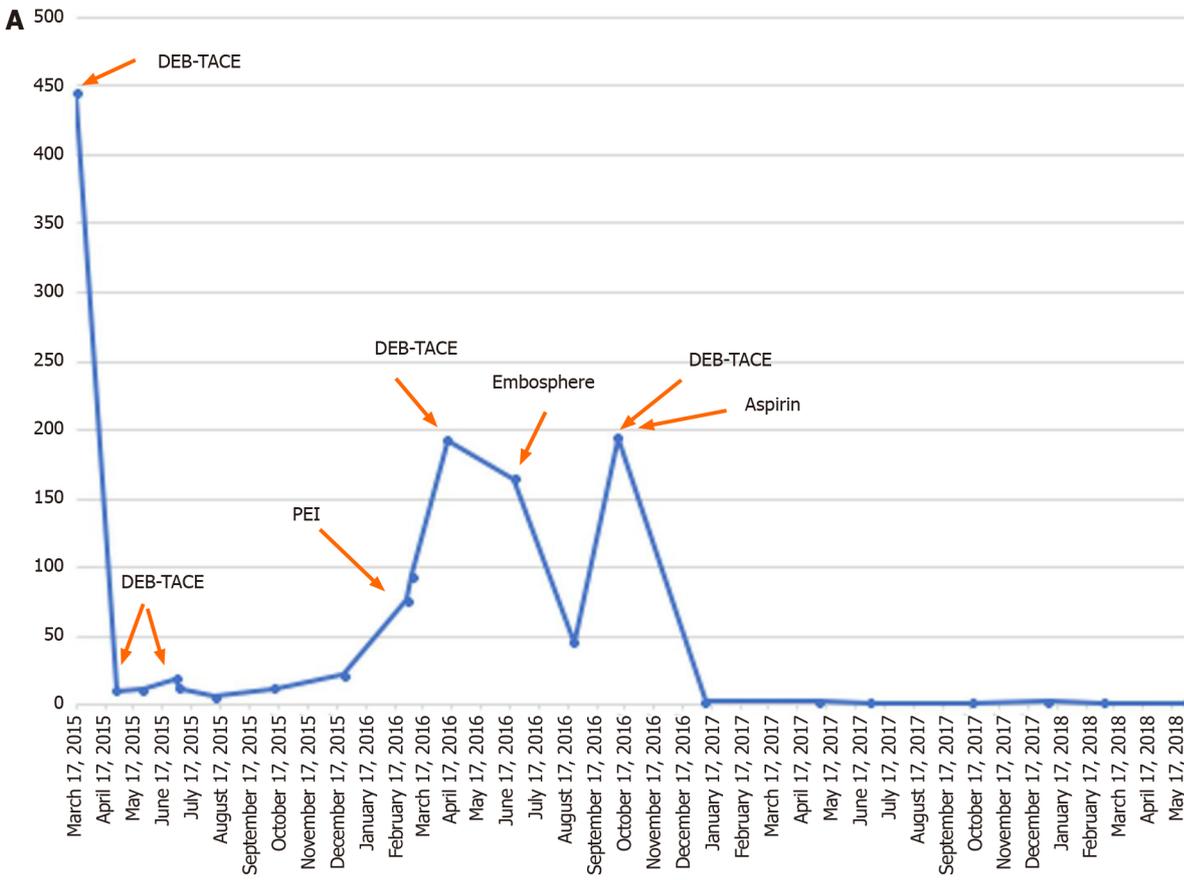
This strategy achieved disease control for almost 5 years until February 2021, as confirmed by magnetic resonance imaging and monitoring of alpha fetoprotein. The treatment was well tolerated (Figure 1A and C).

DISCUSSION

HCC is a highly heterogeneous disease[8]. The etiology of HCC in Chinese individuals is mainly chronic hepatitis B virus infection, which is quite different to that in European patients, for whom HCC is caused mainly by alcohol and chronic hepatitis C virus infection[2]. Due to the differences in etiology and ethnicities, the driving genes in HCC must be different globally. According to our data, APC mutations were among the top 20 most frequent mutations. However, in the COSMIC database, APC mutations are very rare, and few APC mutations related to HCC have been reported [6]. In the present case, we found an APC mutation that triggered HCC. The effects of this mutation could be consistently suppressed by aspirin. Thus, APC mutation-triggered HCC might be a new subgroup of chronic hepatitis B virus infection-related HCC. Wnt pathway inhibition could be an effective remedy for this subgroup of patients.

The Wnt pathway has been reported to be very important in the development of malignancies[9]. Approximately 20% of HCC patients reportedly display Wnt pathway activation[5]. The causes of Wnt pathway over-activation are complex. The importance of Wnt over-activation in the development of HCC could differ from one patient to another, which might not be evident in a large cohort study. Thus, the Wnt inhibitor failed to show reliable efficacy among non-selected HCC patients. In the present case, an APC mutation triggered HCC and the Wnt pathway was exclusively activated by APC dysfunction, as other elements of the Wnt pathway were not mutated. Knowledge of the Wnt pathway and its association with the COX2 pathway has led to the use of COX2 inhibitors[7], including the COX inhibitor aspirin and the selective COX2 inhibitors celecoxib and meloxicam, which are clinically available. In the present case, we chose aspirin and achieved long-term disease control.

The diagnosis of HCC does not rely on a pathologic test[2], which decreases the availability of RNA sequences in tumor tissues. The lack of tumor tissue gene mutation information, especially for advanced and recurrent diseases, has limited the extensive application of precisely designed targeted therapy based on dominant driver genes. Thus, needle biopsy might be of potential benefit for advanced and recurrent HCC. The present case demonstrates that RNA sequencing of HCC tissues might be a valuable approach and that the current HCC diagnostic procedure without histological tests might be insufficient for precise targeted therapy.



Changes in AFP levels during treatment

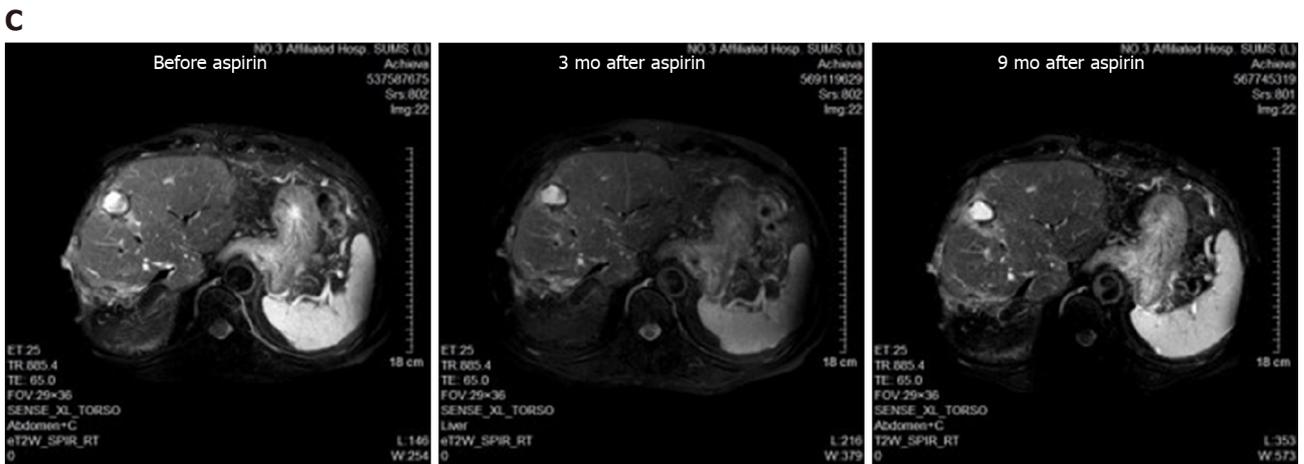
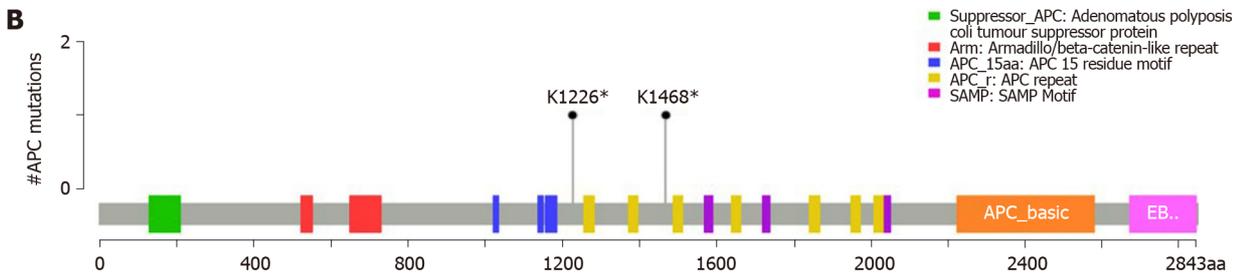




Figure 1 Patient information. A: Changes in alpha fetoprotein during treatment. B: Mutation map of adenomatous polyposis coli domains; C: Changes in tumor masses by magnetic resonance imaging before and after aspirin treatment. APC: Adenomatous polyposis coli; TACE: Transcatheter arterial chemoembolization.

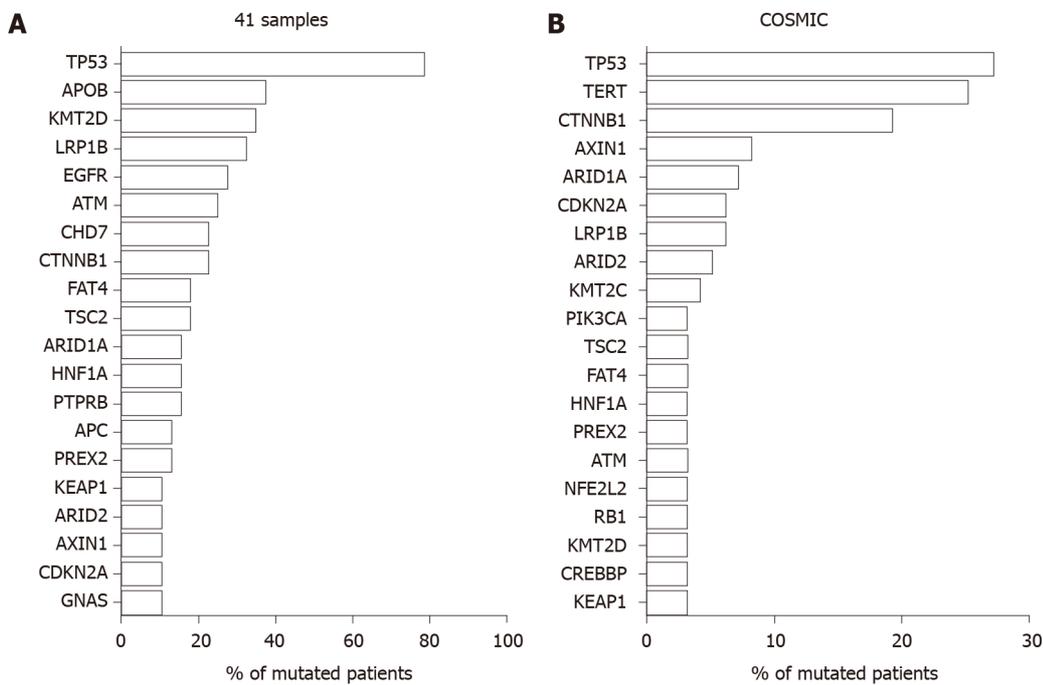


Figure 2 Gene mutation profiles. A: Patients with hepatitis B-related hepatocellular carcinoma (HCC, *n* = 41); B: Global HCC population from the Catalogue of Somatic Mutations in Cancer database. COSMIC: Catalogue of Somatic Mutations in Cancer database.

CONCLUSION

In the present case, the success of aspirin treatment was based on the dominant genetically driven Wnt pathway and exclusive mutation of APC among all the Wnt pathway elements, as discovered by RNA sequencing.

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