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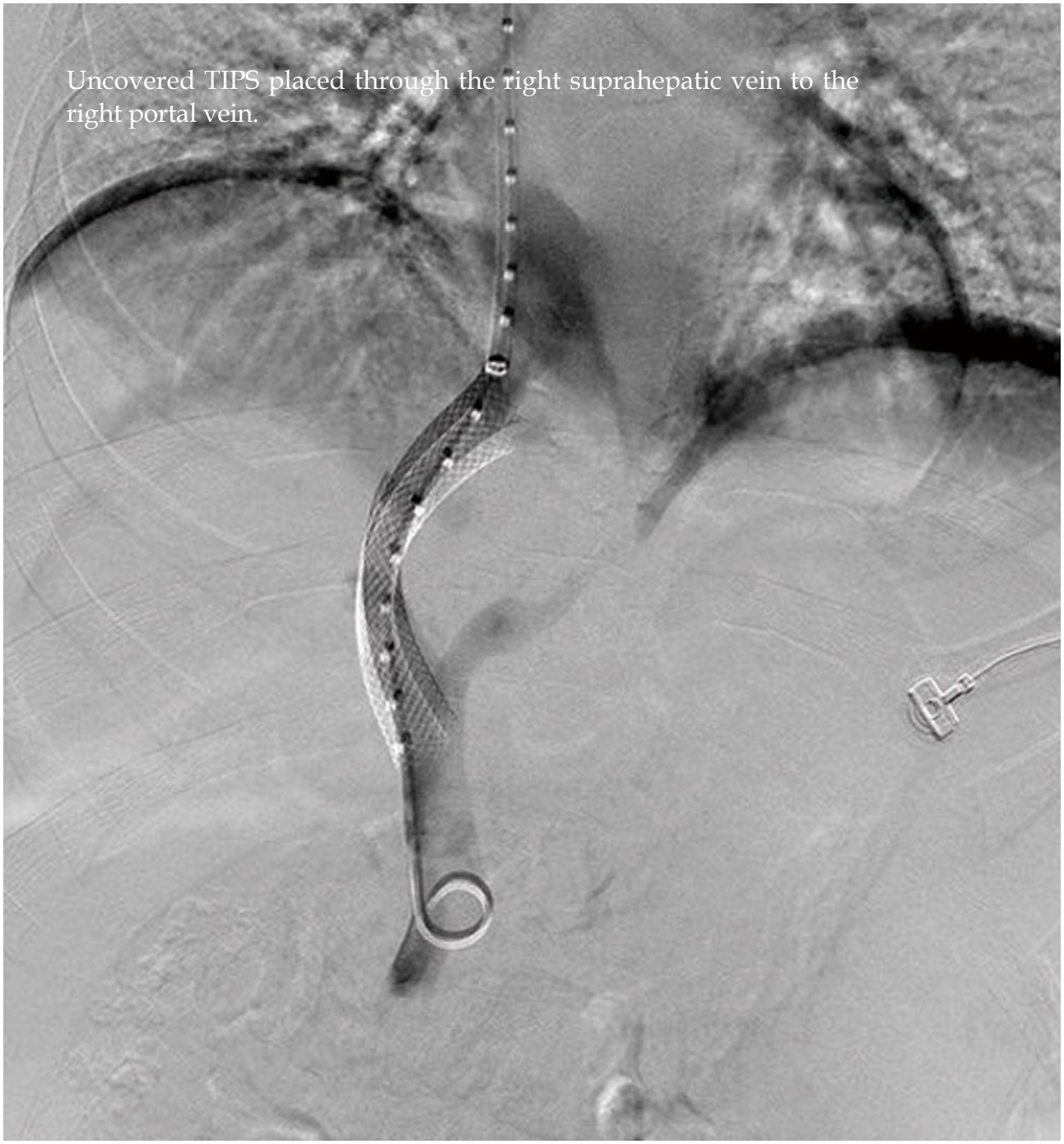

Uncovered TIPS placed through the right suprahepatic vein to the right portal vein.

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EDITORIAL

Combination drug treatment in patients with non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) includes simple steatosis, a benign condition, and non-alcoholic steatohepatitis, a condition that beyond TG accumulation also includes necroinflammation and fibrosis. An association between NAFLD and cardiovascular disease (CVD) has been recently suggested. NAFLD patients usually have an increased CVD risk profile. NAFLD is also associated with metabolic syndrome (MetS) and is considered as the hepatic component of MetS by some authors. Currently, the only established treatment of NAFLD is gradual weight loss. However, multifactorial treatment of NAFLD risk factors may be needed to reduce the increased CVD risk of NALFD patients. Drug combinations that include antiobesity drugs (such as orlistat and sibutramine) and target CVD risk factors may be a good approach to NAFLD patients. Our group has investigated the orlistat-fenofibrate combination treatment in obese patients with MetS and the orlistat-ezetimibe and sibutramine-antihypertensive combination treatment in obese patients with hyperlipidaemia with promising results in CVD risk factor reduction and improvement of liver function tests. Small studies give promising results but double-blind, randomized trials examining the effects of such multifactorial treatment in hard CVD endpoints in NAFLD patients are missing.

Key words: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Treatment; Orlistat; Sibutramine; Fenofibrate; Ezetimibe; Weight loss

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) ranges from pure fatty liver alone, a benign condition characterized by triglyceride (TG) accumulation in hepatocytes, to non-alcoholic steatohepatitis (NASH), a condition that beyond TG accumulation also includes necroinflammation and fibrosis, and to end stage liver disease and liver cancer[1,2]. Insulin resistance (IR) is considered to play central role in the pathogenesis of NAFLD[3-7]. IR results in hyperinsulinaemia and high levels of plasma free fatty acids which enter into the hepatocyte cytoplasm to produce TGs. TG accumulation in hepatocytes results in hepatic steatosis[1]. Natural history studies show that up to 16% of patients with NASH may progress to cirrhosis and some of these patients will develop end-stage liver disease and/or possibly hepatocellular carcinoma necessitating liver transplant[8].

An association between NAFLD and cardiovascular disease (CVD) has been recently suggested[9,10]. NAFLD patients have increased subclinical atherosclerosis compared with non-steatosic individuals[9]. NAFLD is also

associated with an increased CVD risk profile[11]. In NAFLD, the liver overproduces several atherogenic factors such as inflammatory cytokines, glucose, lipoproteins, coagulation factors and factors that increase blood pressure[11]. Furthermore, in Koreans it has been shown that elevated alanine aminotransferase (ALT) levels are independently associated with increased CVD or diabetes-related mortality[12]. Thus, elevated ALT levels, as a marker for NAFLD, may serve as a surrogate predictor of CVD or diabetes-related mortality.

NAFLD is also associated with metabolic syndrome (MetS) and is considered as the hepatic component of MetS[6,13-15] by some authors. In a recent study of 1003 people of whom 225 (22.6%) had NAFLD, the prevalence of MetS was significantly greater (47%) among cases compared with control subjects (23%)[16].

The prevalence of NAFLD is expected to rise owing to the increasing prevalence of obesity and MetS world-wide. Currently the only established treatment of NASH is gradual weight loss. Many studies show that dietary intervention or bariatric surgery in patients with biopsy-confirmed NASH can be effective in improving not only liver function tests (LFTs) but also liver histology[17-19]. Multifactorial treatment of NAFLD risk factors may be needed to achieve the best results. In a prospective, open-label, randomized study, 186 non-diabetic patients with MetS and both biochemical and ultrasonographic evidence of NAFLD received lifestyle advice and treatment for hypertension (mainly inhibitors of the renin-angiotensin system), impaired fasting glucose (metformin), obesity (orlistat) and dyslipidaemia [randomly allocated to atorvastatin 20 mg/d or micronised fenofibrate 200 mg/d or both drugs] for 54 wk[20]. At the end of the treatment, 67% of patients on atorvastatin, 42% on fenofibrate and 70% on combination treatment did not have biochemical plus ultrasonographic evidence of NAFLD ($P < 0.05$ *vs* baseline for all comparisons)[20]. In this context, drug combinations that include antiobesity drugs (such as orlistat and sibutramine) and target CVD risk factors may be a good approach for NAFLD patients.

There is evidence that weight loss induced by orlistat reverses fatty infiltration and improves hepatic fibrosis in obese patients with non-alcoholic steatohepatitis[21]. Moreover, in another study, 50 overweight subjects with non-alcoholic steatohepatitis (proven with biopsy) were randomized to receive a 1 400 Kcal/d diet plus vitamin E (800 IU) daily with or without orlistat (120 mg tid) for 36 wk[22]. Subjects who lost ≥ 5% of their body weight experienced an improvement in insulin resistance and steatosis whereas those who lost ≥ 9% experienced an improvement in hepatic histologic findings[22].

Our group assessed the effect of orlistat and fenofibrate, alone or in combination, in overweight and obese patients ($n = 89$) with MetS[23] in an open-label randomised study (the FenOrli study). At the end of the 6 mo treatment period, only 54% of patients in the orlistat group, 46% in the fenofibrate group and 29% in the combination group still met the MetS diagnostic criteria ($P < 0.01$ *vs* baseline in all treatment groups)[24]. Furthermore, after 6 mo of treatment, significant in-group changes were observed for body weight, body mass index (BMI) and waist circumference in all treatment groups but these reductions were more pronounced in groups receiving orlistat[24]. There were significant in-group reductions in plasma lipid levels. Specifically, the reductions of total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) levels were significantly greater in the combination group compared with monotherapy. Furthermore, glucose, insulin and homeostasis model assessment (HOMA) index levels were improved after the 6 mo treatment significantly more in groups receiving orlistat compared with fenofibrate administration. Aspartate aminotransferase and ALT activities were not significantly altered in either group. However, gamma-glutamyl transpeptidase (GGT) activity was significantly reduced in all 3 groups. This effect may be clinically relevant since GGT activity, even within its reference range, is associated with CVD risk factors[25]. Furthermore, an increase in serum GGT activity may predict the onset of MetS, incident CVD and death[26]. Furthermore, at 6 mo, fenofibrate and combination treatment groups experienced a greater reduction in small dense LDL-C (sdLDL-C) levels (-63% and -77% respectively)[24], which are considered the most atherogenic LDL particles[27].

Our group also investigated, in an open-label randomised trial, the effects of orlistat and ezetimibe, alone or in combination, in 86 overweight and obese patients with hypercholesterolemia (TC > 200 mg/dL)[28]. Reductions in BMI, waist circumference, and body weight at 6 mo were significantly greater in groups receiving orlistat compared with ezetimibe monotherapy. At the end of the 6 mo treatment period, a significant improvement in lipid profile was observed in all groups which was significantly greater in the combination group compared with either monotherapy[28]. Glucose, insulin and HOMA index levels were improved after the 6 mo treatment significantly more in groups receiving orlistat compared with ezetimibe administration. ALT and GGT activities improved in all treatment groups. The reduction in GGT activity was significantly greater in the combination group compared with either monotherapy[28]. There were also significant reductions in sdLDL-C concentration in all treatment groups which were more pronounced in the combination group[28].

Another antiobesity drug useful for NAFLD is sibutramine[29]. In a recent study we examined the effect of sibutramine together with verapamil slow release/trandolapril (VeTra) combination tablet *vs* VeTra alone in obese hypertensive patients[30]. The combination treatment resulted in greater reductions of BP (significant only for diastolic BP) compared with the antihypertensive treatment alone at 6 mo, with no significant change in heart rate in any group[30]. The combination treatment led to significant improvements in the lipid and carbohydrate metabolism variables. ALT activity was significantly

decreased only in the combination group in our study. This may be associated with a decrease in liver fat content[31].

We also showed successful results in reversing metabolic syndrome in obese patients with MetS receiving combination of fenofibrate and the recently withdrawn rimonabant[32]. The combination treatment resulted in a significant reduction in the number of metabolic syndrome criteria compared with that of fenofibrate monotherapy ($P < 0.05$)[32].

These results are promising for patients with obesity and MetS of whom a significant percentage has NAFLD. However, it should be mentioned that, although modest elevation of LFTs may raise the suspicion of NASH, none of these tests are sensitive enough to establish the diagnosis of NASH with great accuracy[33]. Furthermore, liver CT or MRI, although sensitive, are not specific enough[34]. Hence, biopsy remains the "gold standard" for the diagnosis of NASH despite several limitations such as cost, the skill required, associated mortality and morbidity as well as sampling variation[1,34].

In summary, patients with NAFLD usually have visceral obesity and present with increased CVD risk. These patients need a multifactorial treatment targeting excess body weight, hyperlipidaemia and hypertension, to reduce CVD risk factors and possibly improve hepatic histology. Small studies give promising results, but double-blind, randomized trials examining the effects of such multifactorial treatment in hard CVD endpoints in NAFLD patients are missing.

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GUIDELINES FOR CLINICAL PRACTICE

Liver function tests: Association with cardiovascular outcomes

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Abstract

An association between nonalcoholic fatty liver disease and cardiovascular disease has been repeatedly reported. Several studies have focused on levels of gamma-glutamyltransferase (GGT) and alanine aminotransferase (ALT) in relation to cardiovascular outcomes. Evidence indicates that GGT may have a potential role for cardiovascular risk stratification while the role of ALT for cardiac prognosis remains controversial. A conceptual framework that includes not only GGT and ALT but also markers of hepatocyte apoptosis such as cytokeratin-18 fragments should be developed.

Key words: Nonalcoholic fatty liver disease; Liver function tests; Cardiovascular disease; Outcomes

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INTRODUCTION

The evidence in favour of an association between nonalcoholic fatty liver disease (NAFLD) and cardiovascular disease is now considerable[1]. For example, NAFLD patients diagnosed on ultrasonographic findings have an increased risk of incident cardiac events[2]. The nature of the association between NAFLD and cardiovascular events has generated a great deal of interest in the scientific community and levels of common biomarkers of NAFLD, including gamma-glutamyltransferase (GGT) and alanine aminotransferase (ALT), have been repeatedly studied in relation to cardiovascular outcomes. The objective of this editorial is to give an overview of the current evidence linking levels of GGT and ALT to cardiac prognosis. The overview provided in this paper is not intended to be exhaustive; rather, a brief summary of some key findings is provided.

CURRENT EVIDENCE

In a previous meta-analysis of 10 population-based cohort studies, it was reported that an increase in 1 unit of log-transformed GGT was associated with an adjusted hazard ratio of 1.34 (95% CI: 1.22-1.48) for incident vascular events[3]. Besides being an early subclinical marker of fatty liver, GGT may act as a marker of oxidative stress and exposure to environmental chemicals[4]. It has thus been suggested that increased GGT levels may be linked to cardiovascular disease *via* different biological processes such as oxidative stress or lifestyle behaviours[3].

In contrast, the association of serum ALT, an enzyme more specific to the liver than GGT, with cardiac outcomes appears more controversial. There are at least six published studies that have addressed the association between serum ALT and incident cardiovascular events[3,5-9]. Figure 1 shows that the results have been quite divergent, casting doubts on an independent association between ALT and incident cardiac events. There are

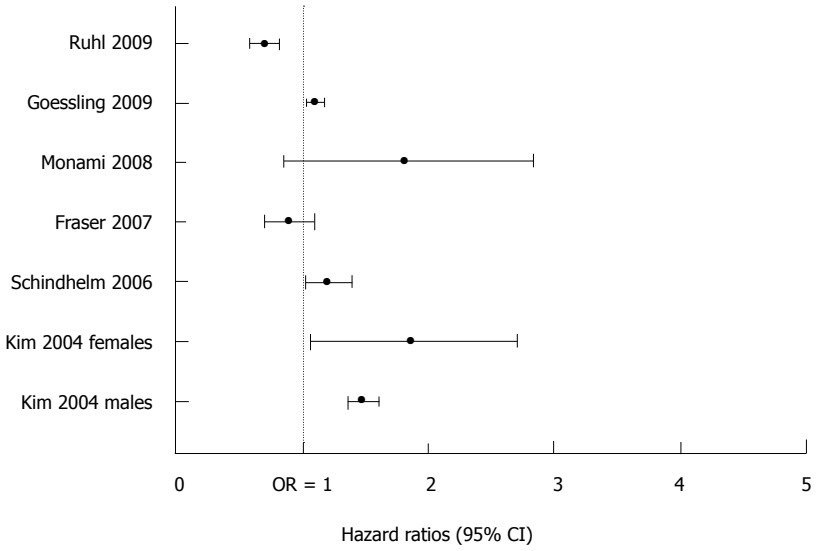

Figure 1 Fully-adjusted hazard ratios and 95% confidence intervals for incident cardiovascular disease for an increase in 1 unit of log-transformed ALT in six published prospective studies. OR indicates odds ratio and CI confidence interval.

several possible explanations for this lack of association. Firstly, significant heterogeneity between studies could have resulted in null findings. Secondly, ALT is not only a marker of NAFLD but also of ectopic fat in general[10]. Finally, the association between ALT and cardiac risk may be confounded by other cardiovascular risk-equivalent such as diabetes[11].

CONCLUSION

In summary, GGT may have a potential role for cardiovascular risk stratification but its predictive power appears modest overall. Evidence suggests that a doubling of GGT is associated with a 34 percent increase in the risk of incident cardiovascular events[3]. In contrast, there is not enough evidence that ALT may predict future cardiovascular events. As scientific evidence is insufficient, more research is needed into the prognostic significance of liver function tests for incident cardiovascular events. In particular, there are a number of issues that should be systematically addressed in the future. For example, it will be necessary to clarify the association with cardiovascular events of elevated GGT or ALT for initially healthy individuals compared with patients with NAFLD diagnosed by ultrasound. Future detailed analysis of the current studies will provide better discrimination on who is at increased risk and who is not. Another open issue is whether there are sex-related effects or relative risks. Even after adjustment for known risk factors, associations of GGT/ALT with cardiovascular events appear stronger in males than in females. A conceptual framework that includes not only classical markers of NAFLD but also markers of hepatocyte apoptosis such as cytokeratin-18 fragments[12,13] or other non-invasive liver tests such as Fibroscan[14] should form the basis for this research agenda.

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REVIEW

Role of radiofrequency ablation in the treatment of small hepatocellular carcinoma

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Abstract

Radiofrequency ablation (RFA), one of the most advanced loco-regional ablative therapeutic methods, is widely utilized in the treatment of hepatocellular carcinoma (HCC). Because of its minimal invasiveness and high efficacy, RFA has been regarded as a curative therapy as alternative to surgical resection and liver transplantation. It brings new hope and a new treatment pattern for small HCC. In this article, we summarize the important role of RFA in the treatment of small HCC according to our clinical experience over six years. The prognosis of small HCC after RFA is comparable to that of surgical resection but with higher safety, less complications, wider applicability, and good long-term survival. RFA will play a more and more important role in the clinical treatment of small HCC.

Key words: Hepatocellular carcinoma; Radiofrequency ablation; Hepatectomy; Prognosis; Complication; Recurrence; Therapy

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world[1]. Although the majority of cases are still found in Asia and Africa, recent evidence has shown that the incidence and mortality rate of HCC are rising in North America and Europe[2,3]. The prognosis of HCC is generally poor. Apart from liver transplantation, partial hepatectomy remains the best hope for a cure but is suitable for only 9% to 27% of patients[4,5]. The presence of significant background cirrhosis often precludes liver resection in patients with HCC. Recurrence of tumor within the liver remnant is also common in patients who have undergone 'curative' liver resection[6].

In the past two decades, percutaneous local ablative therapy has emerged as a safe and effective treatment for small HCC[6]. Of the various percutaneous local ablative therapies, radiofrequency ablation (RFA) has attracted the greatest interest because of its effectiveness and

safety for small HCC ≤ 5.0 cm, with a 3-year survival rate of 62% to 68%, a low treatment morbidity of 0% to 12%, and a low treatment mortality of 0% to 1%[6-11]. RFA now is regarded as a curative therapy for small HCC (sHCC) as alternative to liver resection and liver transplantation. The present article is focused on the percutaneous use of RFA in the treatment of sHCC.

PRINCIPLE AND DEVELOPMENT OF RFA

RFA is a physical thermal ablation technique. The goal of RF ablation is to induce thermal injury to the tissue through electromagnetic energy deposition. In RF ablation, the patient is part of a closed-loop circuit, that includes a RF generator, an electrode needle, and a large dispersive electrode (ground pads). An alternating electric field is created within the tissue of the patient. Because of the relatively high electrical resistance of tissue in comparison with the metal electrodes, there is marked agitation of the ions present in the target tissue that surrounds the electrode, because the tissue ions attempt to follow the changes in direction of alternating electric current. The agitation results in frictional heat around the electrode. The discrepancy between the small surface area of the needle electrode and the large area of the ground pads causes the generated heat to be focused and concentrated around the needle electrode. The local temperature can reach to 90-120℃, which leads to immediate tissue death and thermal coagulation necrosis, thereby destroying the tumor[12].

Three stages can be defined in the development of RFA since its first application in clinical treatment for HCC, according to the development of radiofrequency electrodes: In the first stage, during the early 1990s, a single and solid-center needle electrode was applied in RFA, and the ablative region was only about 1.6 cm in diameter. It utilization was very restricted because of the limitation of ablative region. During the second stage, in the middle 1990s, the electrode had been greatly upgraded. A multiple electrode, the LeVeen electrode (Radiotherapeutics) and an internally cooled needle electrode (Radionics) were invented. Both increased the ablative region to 3.5-5.0 cm in diameter, dramatically improving the therapeutic efficacy and resulting in RFA becoming widely applied in treatment of HCC. RFA gradually became the preferred method for local ablative therapies and attracted more and more attention. In the current third stage a new generation electrodes is being developed on the base of the second-generation electrodes. Most of them have integrated two-different mechanisms, such as a combined cluster needle electrode and saline enhanced electrode. For example, Celon Power (Olympus) has integrated 2-3 kinds of mechanism from second-generation electrodes, resulting in a further increase in the ablative region to 5.0-7.0 cm in diameter. Furthermore, by applying multi-electrode ablation systems and locating the electrodes according to tumor shape; precise "conforming ablation" may be achieved. All these developments will further improve the therapeutic efficacy of RFA.

EFFICACY AND SAFETY OF RFA FOR SHCC

In 1995, Rossi *et al*[13] in Italy firstly introduced RFA as a palliative therapy for HCC. In the middle 1990s, the appearance of the second-generation electrode made RFA widely utilized and attracted more and more attention to the technique. RFA was considered to be a "potential curative" therapy for sHCC. In 1996 the long term survival rates of RFA for sHCC were first reported by Rossi S *et al*[14]. In their study, 39 patients with sHCC ≤ 3.0 cm in diameter were treated with percutaneous RFA, with overall 1-, 3- and 5-year survival rates of 97%, 68% and 40%, respectively. Since then, more and more studies about RFA in the treatment of sHCC have been reported with gradually improving results. Most results showed that RFA was almost as effective as liver resection for sHCC. In the largest study to reported by Tateishi *et al*[15] in 2005, 303 patients with HCC ≤ 5.0 cm in diameter were included, and the 1-, 3- and 5-year survival rates were 93.0%, 74.3% and 45.2%, respectively[8].

Tumor size, location and stage, Child-Pugh class and so on are considered contribute to the prognosis of sHCC after RFA[16]. Tumor size seems to be the most important factor. A study reported by Livraghi *et al*[17] showed that the complete ablation rate of HCC after RFA declined dramatically with increasing tumor diameter. The complete ablation rate was ≥ 90% when tumor was ≤ 3.0 cm in diameter, but sharply decreased to 71% and 25% for tumor 3.1-5.0 cm and > 5.0 cm. So for HCC ≤ 3.0 cm, complete ablation can be reached by RFA alone, whilst for HCC 3.0-5.0 cm, RFA combined with other therapies or multiple overlapping ablation methods appear to be necessarily[15].

Various reports have shown the safety of RFA in the treatment of HCC. A study[18] including 2320 patients with 3530 HCC tumors reported that the mortality rate after RFA was 0.3%. The major complications rate was 2.2%, including bleeding, tumor implantation, hepatic abscess, enterobrosis, whilst the minor complications rate was 4.7%, including fever, pain, skin burning, and pleural effusion. The number of ablation sessions was the major factor which contributed to complications. Thus, diminishing ablation sessions was the most important ways of decreasing complications[18]. RFA was previously considered contraindicated for HCCs located on the surface of the liver, or close to vital organs, large vessels. However, in past decade, with the development of equipment and improvement of techniques, these types of HCCs were also reported to have been treated with RFA safely. So we believe that RFA may now be safely performed whenever patients have good preserved liver function.

RFA can be guided by different methods, such as ultrasound, computer tomography, laparoscopy or laparotomy. The percutaneous method is much less invasive than other methods. It allows patients to recover more rapidly and can even be performed in the day-surgery clinic. However, there may be some tumors where it is difficult to perform RFA percutaneously or where there is a risk of adjacent organs burning. For laparoscopy or laparotomy RFA, it was easy to gain entry, protect adjacent organs, and furthermore enlarge the ablative region by use of hepatic inflow blood clamping. However, this was much more invasive and required a longer hospital stay. Reports[18] have shown that open RFA may contribute to high a complete necrosis rate and low local recurrence rate, although it involved more complications and risks. Therefore, the percutaneous method is the preferred method, whilst the laparoscopy or laparotomy method can be carried out when the percutaneous method is difficult or where there is risk of adjacent organs burning.

RFA VERSUS OTHER LOCAL ABLATIVE THERAPIES FOR SHCC

Clinical trials comparing RFA with PEI demonstrated the clear superiority of RFA[19-23]. Livraghi *et al*[19] reported the first prospective nonrandomized comparative study of these 2 techniques in 1999. RFA resulted in a higher rate of complete necrosis (90% *vs* 80% of tumors) and required fewer treatment sessions (mean, 1.2 *vs* 4.8 sessions) than PEI. However, the complication rate was higher with RFA than with PEI. Since then, these 2 techniques were further evaluated in a randomized trial setting. In the RCT of Lencioni *et al*[20], RFA was superior to PEI in local recurrence-free survival. The 1- and 2-year local recurrence-free survival rates were 98% and 96% in the RFA group and 83% and 62% in the PEI group, respectively. Lin *et al*[21] performed a RCT comparing RFA with PEI and percutaneous acetic acid injection (PAI) in patients with HCC less than 3 cm in diameter. RFA was superior to PEI and PAI in local recurrence, overall survival, and cancer-free survival rates. However, RFA resulted in significantly more major complications than PEI or PAI. Major complications occurred in 4.8% of patients in the RFA group and in none of the other 2 groups. In another RCT, Lin *et al*[22] compared RFA with conventional PEI regimens and with high-dose PEI regimens, and showed RFA required fewer treatment sessions to completely ablate tumors. RFA was also associated with a significantly lower rate of local tumor progression, and higher overall and disease-free survival. In the RCT of Shiina *et al*[23], RFA resulted in a 46% decreased risk of death, a 43% decreased risk of overall recurrence, and an 88% decreased risk of local tumor progression when compared with PEI. There was no significant difference in the complication rates between the 2 groups of patients.

The superiority of RFA over MCT was supported by the RCT of Shibata *et al*[24]. In this study, 72 patients with 94 HCC nodules were randomly assigned to RFA and MCT. Both groups showed similar therapeutic effects, complications, and residual disease rate. However, the number of treatment sessions per nodule was significantly lower in the RFA group than in the MCT group (1.1 *vs* 2.4). Complete therapeutic effect was achieved in 46 (96%) of 48 nodules treated with RFA and in 41 (89%) of 46 nodules treated with MCT[24].

RFA VERSUS LIVER RESECTION FOR SHCC

Liver resection remains the gold standard therapy for sHCC. However, the presence of significant background cirrhosis often precludes liver resection for sHCC especially in China, and the 5-year recurrence rate after liver resection is as high as 43.5%. In recent decades, RFA has emerged as a new treatment modality and attracted great interest because of its effectiveness and safety for sHCC, with a 3-year and 5-year survival rate of 50% to 80%, 40%-60%, respectively, and a 5-year recurrence rate of 40%-50%. This has challenged the role of liver resection. Recently, we conducted a RCT on 180 patients with a solitary HCC $\leqslant$ 5 cm who received either percutaneous RFA or surgical resection[10]. This RCT showed percutaneous RFA to give similar overall and disease-free survivals as surgical resection for patients with solitary and small HCC. The 1-, and 4-year overall survival rates after percutaneous RFA and surgery were 95.8%, 67.9% and 93.3%, 64.0%, respectively. The corresponding disease-free survival rates were 85.9%, 46.4% and 86.6%, 51.6%, respectively. As a less invasive procedure, percutaneous RFA had the advantage over liver resection in giving better short-term postoperative results. There were, however, some limitations in our study as the sample size was small and the follow-up was not sufficiently long term. It is, therefore, still unclear whether or not RFA can actually replace surgery in the treatment of sHCC and a large sample, multi-center prospective randomized trial is needed. We believe that RFA could at least partly replace liver resection in the treatment of sHCC, especially for center tumors or recurrent tumors.

Compared to liver resection, RFA has showed some advantages: (1) Minimally-invasive; It takes about ten minutes to ablate a tumor $\leqslant$ 3.0 cm completely, and patients recover in a few days, which is much better than liver resection; (2) No significant impact on liver function and quality of life; (3) Safety; The mortality is only 0% to 1% and mobility 2.2% to 4.7%; (4) More indications: Patients with multi-nodule HCC or deranged liver function are still suitable for RFA; (5) Easily repeatable: Making it available for multi-nodule or recurrent HCC; (6) Cost-effectively: The procedure can wvwn be performed even in the day clinic; and (7) Necrosis tumor tissue also can serve as an autologous vaccine, which will enhance the immune response to cancer.

RFA COMBINED WITH OTHER THERAPIES FOR SHCC

A major limitation of RFA is the small volume of tumor that it can treat. The rate of complete ablative necrosis decreases with the size of the tumor, particularly for those larger than 3 cm. There is general consensus that complete response of RFA therapy in patients is associated with improved outcome. Therefore, initial complete tumor necrosis should be considered a relevant therapeutic target irrespective of tumor size and liver functional status. It has been suggested that a larger area of coagulative necrosis could be created if RFA was performed in HCC after occlusion of the arterial supply or in combination with another ablative therapy.

RFA combined with TAE has been widely utilized to date, and the results are encouraging. During TAE, the tumor feeding arteries are embolized and the blood infusion thereby reduced. This diminishes the "heat sink" effect during the following RFA. Furthermore, this combined therapy not only increases the ablative region, but also destroys the potential microscopic tumors by TAE. In the RCT of Cheng *et al*[25] on sHCC, patients were randomly assigned to treatment with a combination of TACE-RFA (n = 96), TACE alone (n = 95), or RFA alone (n = 100). During a median follow-up of 28.5 mo, the median survivals were 24 mo in the TACE group (3.4 treatment courses), 22 mo in the RFA group (3.6 courses), and 37 mo in the TACE-RFA group (4.4 courses). The rate of objective response sustained for at least 6 months was higher in the TACE-RFA group (54%) than either the TACE alone (35%) or the RFA alone (36%) groups. The authors concluded that TACE-RFA was superior to TACE alone or RFA alone in improving survival for patients with HCC larger than 3 cm. More RCTs with survival data are needed to validate these techniques.

RFA combined with PEI is another effective method. PEI had been utilized in the treatment of HCC for a long time. It usually requires to be repeated several times and with the disadvantages of long treatment cycle, high local recurrence rate etc. During RFA combined with PEI therapy (PEI followed by RFA) the injected ethanol embolizes vessels $\leqslant$ 5mm, so that blood infusion is reduced. Meanwhile, the ethanol can disperse to areaa which RFA failed to reach , such as perivascular tumors. In this way, the ablative effect is enhanced. In our RCT[26], 133 patients were randomly assigned to receive RFA-PEI (n = 66) or RFA alone (n = 67). The 5-year overall survival rates for the RFA-PEI group and the RFA alone group were 49.3% and 35.9%, respectively. The RFA-PEI offered significant survival advantage over RFA alone for patients with tumors of 3.1 to 5 cm in diameter, but not for those with tumors equal or less than 3.0 cm in diameter, or for those with tumors 5.1 to 7 cm in diameter. Moreover, some reports have suggested that RFA combined with injection of cytotoxic drugs will improve the efficacy although this remains to be proved. Combination of different loco regional therapies is a simple, easy way to improve prognosis.

In conclusion, RFA offers a new option for sHCC, and the initial results are encouraging. RFA is more effective than the other modalities of local ablative therapy. It has been shown to achieve effective and reproducible tumor destruction with acceptable morbidity. RFA is accepted as the best therapeutic choice for patients with early stage HCC when resection or transplantation is precluded. Moreover RFA can be used as an alternative treatment to surgery for resectable HCC of less than or equal to 3 cm in diameter. However, more long-term outcomes and prospective randomized control trials are needed to define the role of RFA in the treatment of sHCC, especially in comparison to liver resection.

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REVIEW

Fucosylation and gastrointestinal cancer

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Abstract

Fucose (6-deoxy-L-galactose) is a monosaccharide that is found on glycoproteins and glycolipids in vertebrates, invertebrates, plants, and bacteria. Fucosylation, which comprises the transfer of a fucose residue to oligosaccharides and proteins, is regulated by many kinds of molecules, including fucosyltransferases, GDP-fucose synthetic enzymes, and GDP-fucose transporter(s). Dramatic changes in the expression of fucosylated oligosaccharides have been observed in cancer and inflammation. Thus, monoclonal antibodies and lectins recognizing cancer-associated fucosylated oligosaccharides have been clinically used as tumor markers for the last few decades. Recent advanced glycomic approaches allow us to identify novel fucosylation-related tumor markers. Moreover, a growing body of evidence supports the functional significance of fucosylation at various pathophysiological steps of carcinogenesis and tumor progression. This review highlights the biological and medical significance of fucosylation in gastrointestinal cancer.

Key words: Fucosylation; Gastrointestinal cancer; Alpha-fetoprotein

INTRODUCTION

Oligosaccharides are one of the most important factors in the posttranslational modification of proteins and lipids. Glycomics, the systematic study of glycans and glycan-binding proteins in various biological systems, is an emerging field in the post-genomics and post-proteomics era[1-3]. It is well known that oligosaccharide structures change during malignant transformation[4]. The remodeling of cell surface glycoproteins and glycolipids through modification of oligosaccharide structures is associated with the biological behavior of tumor cells[5-8]. Fucose is a constituent of oligosaccharides, and is notably associated with cancer and inflammation[9]. In the 1980s, the development of monoclonal antibodies against carbohydrate antigens triggered research to detect cancer-associated aberrant glycosylation. Several antibodies recognizing fucosylated glycoproteins or glycolipids in the sera of patients with cancer have long been used as tumor markers, such as CA19-9[10]. Alpha-fetoprotein (AFP)-L3 fraction, which is fucosylated AFP, has also been clinically used as a tumor marker for hepatocellular carcinoma (HCC) since 1996 in Japan and 2005 in the United States[11,12]. In recent years, advances in the methodology for detection of glycan alteration in cancer cells and sera of patients with cancer have driven the development of various types of tumor markers. In this review, we summarize the history of fucosylation-

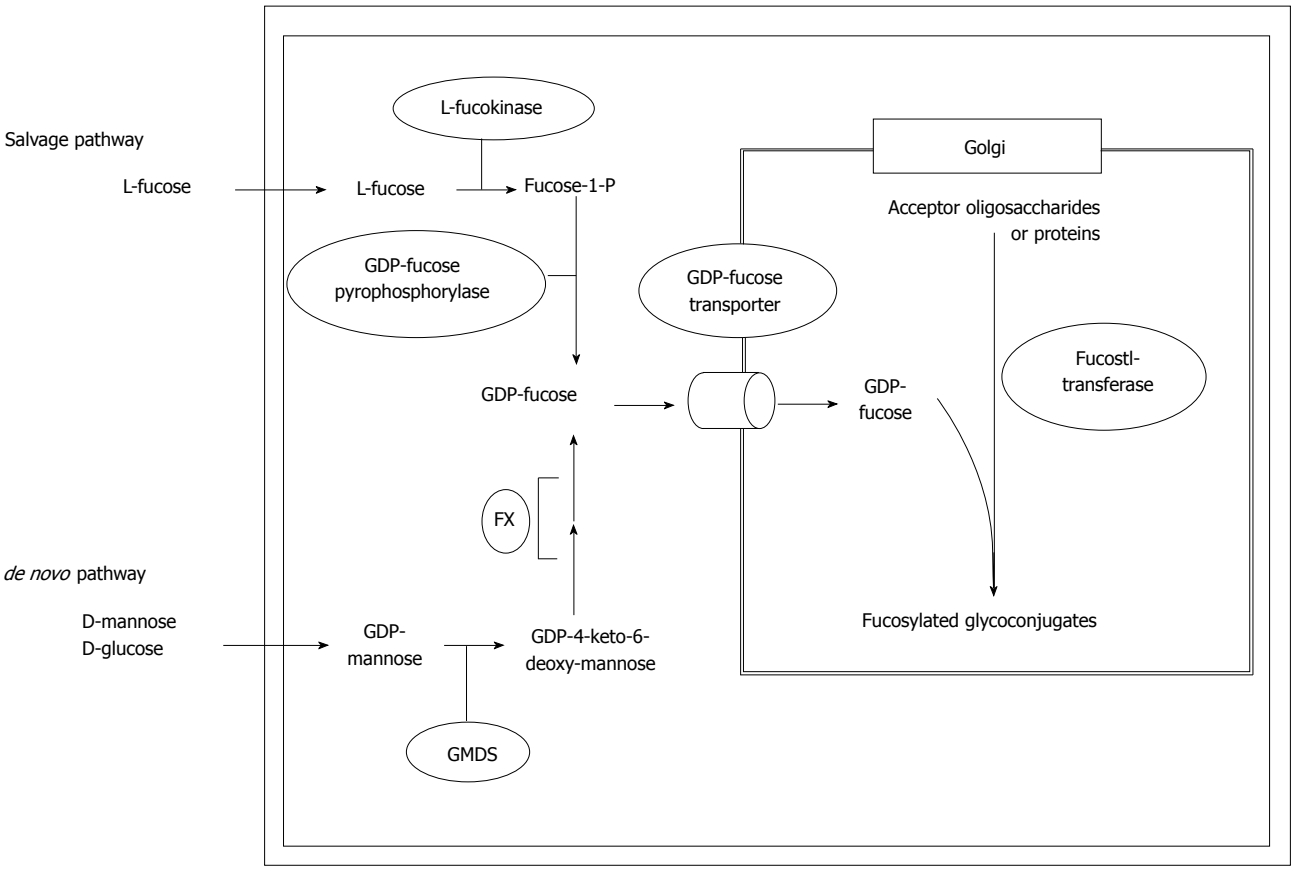

Figure 1 Fucose metabolism. GDP-fucose is mainly synthesized through the de novo pathway by three reactions catalyzed by GDP-4,6-dehydratase (GMDS) and GDP-4-keto-6-deoxy-mannose-3,5, epimerase-4-reductase (FX). Free L-fucose is converted to GDP-fucose through the salvage pathway, which is a minor pathway. GDP-fucose is subsequently transported from the cytosol to the Golgi lumen by GDP-fucose transporter, and then transferred to acceptor oligosaccharides and proteins by fucosyltransferases.

related tumor markers. Moreover, several research groups, including ours, have revealed the biological roles of fucose in several types of cancer. This review also focuses on the pathophysiological significance of fucosylation in gastrointestinal cancer.

REGULATORY MECHANISM FOR FUCOSYLATION

Fucosylation is catalyzed by fucosyltransferases, guanosine 5'-diphosphate (GDP)-fucose synthetic enzymes, and GDP-fucose transporter(s) (Figure 1). The thirteen fucosyltransferase genes which have thus far been identified in the human genome can be divided into five groups. Firstly, FUT1 and FUT2 have been shown to be responsible for the α1-2 linkage of fucose[13,14]. Secondly, a family of α1-3 fucosyltransferases, including FUT3[15], FUT4[16-18], FUT5[19], FUT6[20,21], FUT7[22,23], and FUT9[24,25], is involved in the synthesis of Lewis blood group antigens. FUTs3-7 can synthesize the sialyl Lewis X (sLe^x) structure, NeuAcα2-3Galβ1-4(Fucα1-3)GlcNAcβ-R, and FUTs3-6 and FUT9 (i.e. not FUT 7) can synthesize the Le^x structure, Galβ1-4(Fucα1-3)GlcNAcβ-R. FUT9 is the enzyme most responsible for the synthesis of Le^x in the brain[26]. Only FUT3 exhibits α1-4 fucosyltransferase activity, resulting in the synthesis of type 1 Lewis antigens such as Le^a [Galβ1-3(Fucα1-4)GlcNAcβ-R], Le^b [(Fucα1-2)Galβ1-3(Fucα1-4)GlcNAcβ-R], and sialyl Le^a [NeuAcα2-3Galβ1-3(Fucα1-4)GlcNAcβ-R]. Thirdly, FUT8 catalyzes the transfer of a fucose residue to the C6 position of the innermost GlcNAc residue of *N*-linked oligosaccharides on glycoproteins to produce core fucosylation[27,28]. Fourthly, it remains to be determined which kinds of fucosyltransferase activity FUT10 and FUT11 have[29]. Finally, protein *O*-fucosytransferases 1 and 2 (Pofut1 and Pofut2, respectively) transfer a fucose residue *via* an α-linkage to serine or threonine within epidermal growth factor (EGF)-like repeats containing an appropriate consensus sequence (C^2-$X_{(4-5)}$-[S/T]-C^3) and thrombospondin type 1 repeats containing a consensus sequence (C-X-X-[S/T]-C-X-X-G), respectively[30-33]. Notch and the ADAMTS superfamily were identified as proteins targeted by Pofut1 and 2, respectively[34-36]. Since these proteins have been reported to regulate carcinogenesis and cancer progression, *O*-fucose may be associated with cancer biology[37-39].

GDP-fucose, which is a common donor substrate to all fucosyltransferases, is synthesized in the cytosol *via* two pathways, namely the salvage pathway and the *de novo*

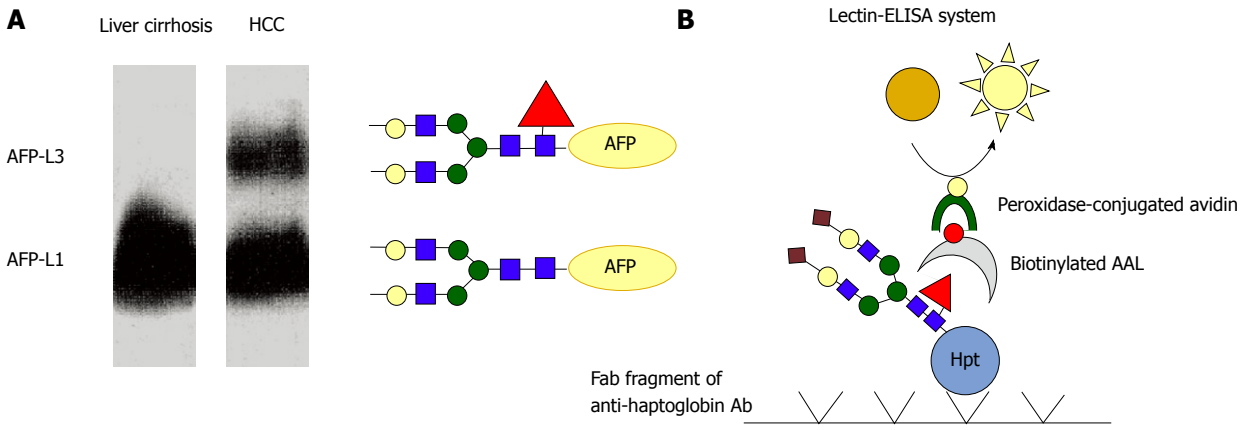

Figure 2 Measurement of fucosylation-related tumor markers in gastrointestinal cancer. A: The sera of patients with liver diseases were electrophoresed on an LCA agarose gel, followed by reaction with anti-AFP antibody. Since LCA specifically binds to fucosylated oligosaccharides on AFP, fucosylated AFP runs slowly on an LCA agarose gel; B: Since IgG has a fucosylated oligosaccharide in its Fc portion, a Fab fragment of anti-human haptoglobin IgG was coated on the bottom of a 96-well ELISA plate. After the sera of patients had been loaded into individual wells, the reaction with biotinylated AAL was performed to detect specifically fucosylated haptoglobin. Peroxidase-conjugated avidin and 3,3',5,5' tetramethylbenzisine were used for development.

pathway. The salvage pathway synthesizes GDP-fucose from free L-fucose, derived from extracellular or lysosomal sources *via* two steps: catalyzation by L-fucokinase[40] and then GDP-fucose pyrophosphorylase[41]. The *de novo* pathway transforms GDP-mannose into GDP-fucose *via* three steps: catalyzation by GDP-mannose-4,6-dehydratase (GMDS)[42,43] and GDP-4-keto-6-deoxymannose-3, 5-epimerase-4-reductase (FX)[44]. The salvage pathway is responsible for only about 10% of the cellular pool of GDP-fucose. Thus, cellular GDP-fucose is mainly produced by the *de novo* pathway. A defect of this pathway leads to a virtually complete deficiency of cellular global fucosylation, including α1-2, 1-3/4, 1-6, and *O*-fucose[42,43,45]. After GDP-fucose has been synthesized in the cytosol, it is transported to the Golgi apparatus through GDP-fucose transporter to serve as a substrate for fucosyltransferases[46,47].

APPLICATION OF FUCOSYLATED GLYCANS AS TUMOR MARKERS

AFP is a glycoprotein produced in the mammalian embryonic liver and is a major serum protein in the developing fetus. While the expression of AFP is absent in the normal adult, its reappearance is observed in patients with HCC. Therefore, AFP has been clinically used as a tumor marker for HCC[48,49]. However, determination of the AFP level is of limited value for the diagnosis of HCC since AFP is often elevated in chronic liver diseases, such as chronic hepatitis (CH) and liver cirrhosis (LC). It is difficult to make a differential diagnosis of HCC from benign liver diseases based on low or moderate elevation of AFP. Under these circumstances, the fucosylated AFP (AFP-L3 fraction) is more effective for the specific diagnosis of HCC because it increases in patients with HCC, but not in ones with CH and LC[11,12] (Figure 2A). LCA (*Lensculinaris agglutinin*) lectin-electrophoresis has been used for the measurement of AFP-L3[50]. Recently, the fully automated and high-performance micro-total analysis system (μTAS) developed by Wako Pure Chemical Industries has increased the analytical sensitivity for AFP-L3 and shortened the measurement time from the 1h required for the conventional assay to less than 10 min[51]. The molecular mechanism underlying the production of fucosylated AFP in HCC is complicated. Fucosylation at an *N*-glycan of AFP is mediated by FUT8, which has been purified and cloned by our group[27,28]. The expression of FUT8 is quite low in the normal liver and increases in HCC[52,53]. The up-regulation of FUT8 expression is required for the production of fucosylated AFP, but such enhancement is insufficient to explain the specific production of fucosylated AFP in HCC due to the broad increased expression of FUT8 in benign liver diseases[54]. We have shown that GDP-fucose is a more important regulatory factor for fucosylation in HCC. The level of GDP-fucose, and the expression of FX and GDP-fucose transporter are significantly increased in HCC tissue compared with that in adjacent chronic inflamed tissue or normal liver tissue[55-57]. As a result of cell experiments, the most important factor for the increase in fucosylation in HCC is thought to be the transport of GDP-fucose. However, a problem is that the level of GDP-fucose is increased only by two or three-fold, which does not explain the fact that the level of serum AFP-L3 is increased in HCC to dozens of times its normal level. Recently, we proposed an additional mechanism by which AFP-L3 increases in sera of patients with HCC[58]. Fucosylated glycoproteins, such as α1-acid glycoprotein and α1-antitrypsin, produced in hepatocytes are secreted into the bile. FUT8 knockout mice show decreased levels of these proteins in their bile, suggesting that fucosylation regulates the secretion of certain types of hepatic fucosylated glycoproteins, including AFP, into the bile. The disruption of this sorting system could be an additional mechanism und-

Table 1 Positive ratio of fucosylated haptoglobin in sera of patients with various diseases[63]

	n	Negative	Positive	%
Normal	30	29	1	3
[a]Pancreatic cancer	87	30	57	66
[a,c]HCC	23	18	5	22
[a,c]Liver cirrhosis	12	9	3	25
[c]Gastric cancer	10	8	2	20
[a]Colon cancer	100	59	41	41
[a,c]Chronic pancreatitis	9	7	2	22

Statistic analysis was performed according to the program for StatView software. [a]$P < 0.05$ *vs* normal; [c]$P < 0.05$ *vs* pancreatic cancer (χ^2 test).

erlying the increase in AFP-L3 in sera of patients with HCC.

Recently, large-scale analytical methods have been developed for the human serum glycoproteome which are also powerful tools for the discovery of diagnostic and therapeutic targets. Glycoprotein (GP) 73 was found to be a novel tumor marker for HCC through lectin-based glycoproteomic analysis[59]. The serum GP73 level was significantly increased in patients with HCC, even in HCC patients who had serum AFP levels less than 20 ng/mL[60]. It has also been reported that the fucosylation of GP73 was increased in patients with HCC[59]. Moreover, other fucosylated glycoproteins, kininogen and α1-antitrypsin, were identified as candidate hepatic tumor markers[61]. The best performance was obtained with the combination of fucosylated kininogen, AFP and GP73, the optimal sensitivity being 95% and the specificity 70%.

Pancreatic cancer is currently one of the leading causes of cancer-related deaths and the overall 5-year survival has been reported to be less than 5%[62]. CA19-9, which is a monoclonal antibody against the sLe^a structure, has been used as a tumor marker for pancreatic cancer[10]. However, false positives are a problem and an early diagnosis based on the CA19-9 level is quite difficult. Under these circumstances, we reported on the potential use of fucosylated haptoglobin as a novel tumor marker for pancreatic cancer[63]. The positive rate for fucosylated haptoglobin is 60%-70% (Table 1) and the rate increases progressively with the stage of the disease. For clinical applications, we established and validated the original lectin-ELISA system (Figure 2B). After our report, several groups reported that fucosylated haptoglobin was increased in sera of patients with lung, prostate, and liver cancer[64-66]. Thus, our established lectin-ELISA system is available for detecting fucosylated haptoglobin in several types of tumors. Haptoglobin is a glycoprotein produced in the liver. Thus, increases in fucosylated haptoglobin in sera of patients with pancreatic cancer are thought to be caused by a soluble factor secreted from pancreatic cancer tissue. Recently, we found that interleukin-6 (IL-6) secreted from pancreatic cancer cells induced the production of fucosylated haptoglobin in the liver[67]. IL-6 could be one of the factors that induce the production of fucosylated haptoglobin in sera of patients with pancreatic cancer.

BIOLOGICAL ROLE OF THE INTERACTION BETWEEN LEWIS ANTIGEN AND SELECTIN IN TUMOR METASTASIS

Inflammation and cancer metastasis are associated with extravasation of leukocytes or cancer cells from blood vessels into tissues. The interaction between cancer cells and vascular endothelial cells is mediated by a coordinated and sequential molecular cascade initiated, in part, by selectins, carbohydrate-binding proteins[68-71]. The initial adhesion mediated by these molecules triggers activation of integrin molecules through the action of several cytokines, leading to the extravasation of cancer cells. In addition, leukocyte-endothelial interactions *via* selectins are associated with tumor angiogenesis and progression[72]. Carbohydrate ligands for selectins, such as sLe^x[73-75] and sLe^a[76,77], are expressed on cancer cells. sLe^x and sLe^a have been used as tumor markers for certain types of cancer. Increases in sLe^x and sLe^a in cancer tissues are correlated with a poor prognosis in several types of cancers, including colon, bladder, and breast cancers[78-80]. Two principal mechanisms underlying the accelerated expression of sLe^x and sLe^a in cancers are known: "neosynthesis" and "incomplete synthesis"[81]. During "neosynthesis", cancer-associated induction of some glycosyltransferases, including fucosyltransferases, has been assumed to influence expression of the determinants. Certain types of fucosyltransferases are up-regulated in cancer tissues, and are responsible for the final step in the synthesis of sLe^a and sLe^x[82,83]. On the other hand, recent results have indicated that normal epithelial cells of several organs contain sufficient amounts of enzymes required for the synthesis of sLe^a and sLe^x. The difference between normal epithelial cells and cancer cells is that normal epithelial cells have additional enzymes to further modify these determinants into more complicated entities, such as disialyl Le^a[84,85] and sialyl 6-sulfo Le^x[86]. The impaired expression of glycosyltransferases, which are involved in the synthesis of complex carbohydrate determinants in normal epithelial cells, leads to the accumulation of less-complex cancer-associated carbohydrates in cancer cells (incomplete synthesis)[87-89].

RELATIONSHIP BETWEEN LEWIS ANTIGEN AND INFECTION BY *HELICOBACTER PYLORI*

Helicobacter pylori (*H. pylori*) is a Gram-negative bacterium that colonizes the human gastric mucosa, and infects over 50% of the world's population[90]. The infection outcome is diverse, and includes the development and recurrence of gastritis, gastric and duodenal ulcers, and an increased risk of gastric adenocarcinomas and

mucosa-associated lymphoid tissue (MALT) lymphomas[91-93]. The lipopolysaccharides (LPSs) of *H. pylori* contain fucosylated oligosaccharides, predominantly type Ⅱ blood group antigens, such as Le^x and Le^y, in addition to minor amounts of type Ⅰ antigens, such as Le^a and Le^b[94,95]. Lewis blood group antigens are also present in the normal human gastric mucosa. The molecular mimicry of host cell surface antigens has been suggested to mask the pathogen from host immune surveillance, and thus plays an important role in colonization and long term infection in the stomach[96]. These Lewis antigens are synthesized by *H. pylori* fucosyltransferases using GDP-fucose as a donor substrate. A recent report suggested that L-fucose released from the surface of host cells by secreted human α-L-fucosidase is used as a source for the production of Le^x in *H. pylori*[97]. Successful *H. pylori* infection is dependent on tight adherence to the mucous epithelial cells and the mucus layer lining the gastric epithelium. Two oligosaccharide structures, Le^b and $sLe^{x/a}$, on the surface of mucous cells serve as specific ligands for blood group antigen-binding adhesin (BabA) and sialic acid-binding adhesin (SabA) respectively, expressed on the surface of *H. pylori*[98,99]. *H. pylori* adhesins, such as BabA, may have evolved an ability to distinguish between host and bacterial ligands based on the differences in their core sugar structures in order to avoid bacterial autoaggregation[100]. These findings show that certain oligosaccharide structures expressed on *H. pylori* and gastric epithelial cells are closely associated with the pathogenesis and prevention of *H. pylori*-related disease, suggesting their therapeutic potential through modification of the determinants.

MODIFICATION OF GROWTH FACTOR RECEPTORS AND ADHESION MOLECULES THROUGH CORE-FUCOSYLATION

Most receptors on the cell surface, including EGF receptor (EGFR), transforming growth factor β receptor (TGFβR), E-cadherin, and integrins, are core-fucosylated. Core-fucosylated oligosaccharides affect protein folding and structure, and as a result, regulate many physiological and pathological events, including cell growth, migration, embryogenesis, and tumor invasion. The importance of core-fucosylation for the functions of several membrane-associated proteins has been demonstrated through glycomic analyses of Fut8-deficient mice. TGF-β is a pleiotropic cytokine that is especially important for cancer biology and the immune system[101,102]. Fut8-deficient mice show marked dysregulation of TGFβR activation and signaling due to impaired binding between a receptor and a ligand[103]. Since TGF-β signaling also controls extracellular matrix homeostasis[104], Fut8-deficient mice show an emphysema-like phenotype in the lungs. Further studies by our group revealed that core-fucosylation was required for the binding of the EGF to EGFR, which contains 12 potential *N*-glycosylation sites[5,105]. The growth retardation observed in Fut8-deficient mice might be caused partly by impaired EGF signaling. Both integrins and E-cadherin are associated with the characteristics of cancer cells through regulation of the cell-extracellular matrix interaction and homotypic cell-cell adhesion, respectively[106,107]. Recent reports showed that a loss or decrease in core-fucosylation on *N*-glycans in integrins and E-cadherin resulted in defects in their functions[6,108]. Thus, core-fucosylation would be closely involved in the biological behavior of cancer cells through regulation of the functions of many membrane-associated proteins.

BIOLOGICAL ROLE OF FUCOSYLATED GLYCANS IN TUMOR IMMUNE SURVEILLANCE *VIA* TRAIL SIGNALING

While many studies have revealed that fucosylation is closely associated with cancer biology through modulation of signal transduction and the cell-cell adhesion pathway, we recently provided new evidence that fucosylation affects tumor immune surveillance *via* another signaling pathway: TRAIL signaling[109,110].

When we examined the global fucosylation level in several colon cancer cells using *Aleuria aurantia* (AAL) lectin, which recognizes fucosylated oligosaccharides, little binding to AAL lectin was found in HCT116 cells (Figure 3A). Further analysis revealed that HCT116 cells had a deleted GMDS transcript which eliminated their ability to synthesize GDP-fucose, and resulted in a virtually complete deficiency of fucosylation. Tranfection of the wild-type GMDS gene into HCT116 cells restored the cellular fucosylation. GMDS-rescued cells showed dramatically suppressed tumor formation and metastasis compared with mock cells when they were inoculated into athymic nude mice (Figure 3B). Depletion of natural killer (NK) cells stimulated tumor growth of the GMDS-rescued cells, but not that of the mock cells, indicating that a deficiency of fucosylation leads to escape from NK cell-mediated tumor immune surveillance (Figure 3C). Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is expressed mainly on the surface of immune cells, where it functions in T-cell homeostasis and NK cell-mediated killing of virally infected or oncogenically transformed cells[111-114]. The engagement of TRAIL receptors by the ligand leads to apoptosis through a specific signaling cascade[115]. Subsequent studies revealed that the GMDS-rescued cells were significantly more susceptible to TRAIL-induced apoptosis (Figure 3D), which caused the increased sensitivity of the GMDS-rescued cells to NK cells. Aberrant transcripts of the GMDS gene were found in three other cancer cell lines (two human colon cancers and one gastric choriocarcinoma) as well as several colon and ovarian cancer tissues. Thus, loss of GMD might be a common mechanism for cancer cells to evade TRAIL-

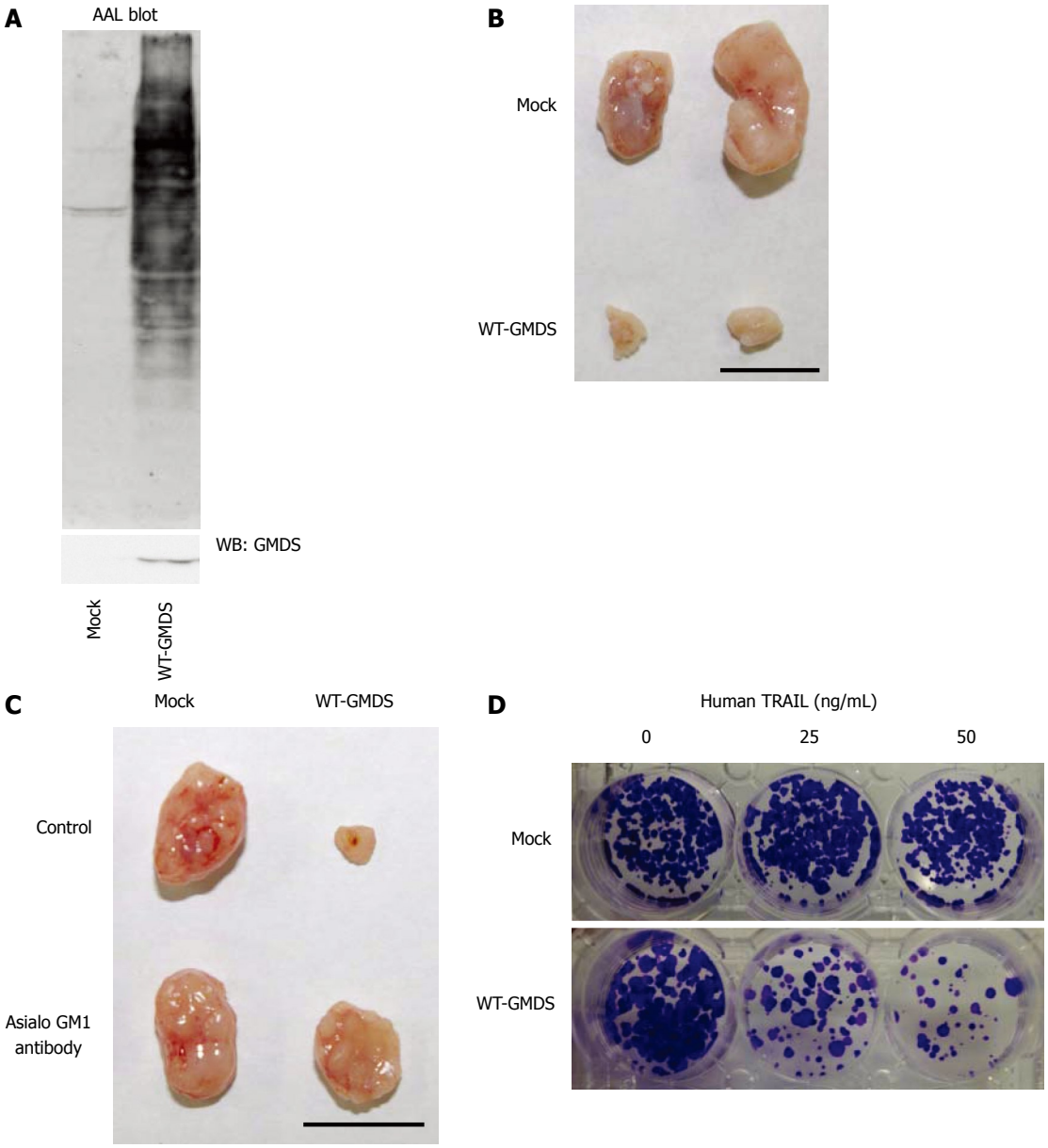

Figure 3 Deficiency of GMDS leads to escape from NK cell-mediated tumor surveillance through modulation of TRAIL signaling[109]. A: After trasnfection of the wild-type GMDS gene into HCT116 cells, Western blot analysis of GMDS and AAL blot analysis were performed. The binding to AAL was restored in transfected cells (WT-GMDS); B: Tumor growth of the GMDS-rescued cells on the backs of athymic nude mice was significantly suppressed compared to mock cells. The bar indicates 10 mm; C: When athymic nude mice were treated with anti-asialo GM1 antibody to deplete NK cells, the tumor growth of the GMDS-rescued cells was accelerated, but not in the case of mock cells. D: The higher susceptibility of the GMDS-rescued cells to TRAIL was confirmed by clonogenic survival assays. These figures are modified from the data in reference 109.

mediated killing. While the increase in fucosylation is important at an early stage of carcinogenesis, defucosylation through genetic mutation in certain types of advanced cancer would lead to escape from NK-cell mediated tumor surveillance and the acquisition of more malignant characteristics (Figure 4).

Currently, because of their ability to kill cancer cells, optimized soluble recombinant human TRAIL or agonistic antibodies targeting TRAIL receptors are undergoing phase 1 or 2 clinical evaluation as promising pro-apoptotic antitumor therapeutic agents in patients with several types of tumors[116]. However, it has now become clear that many types of tumor cells are resistant to TRAIL[117-119]. Thus, studies are now underway to identify and characterize potential biomarkers of sensitivity to TRAIL. Our findings demonstrated that examination of the fucosylation levels in tumor tissues might be promising for predicting the efficiencies of TRAIL-targeted therapies. Furthermore, the combination of TRAIL-targeting medicine with a therapy, which could up-regulate fucosylation level, might have a synergistic therapeutic effect.

CONCLUSION

Fucosylation has been thought to play important roles

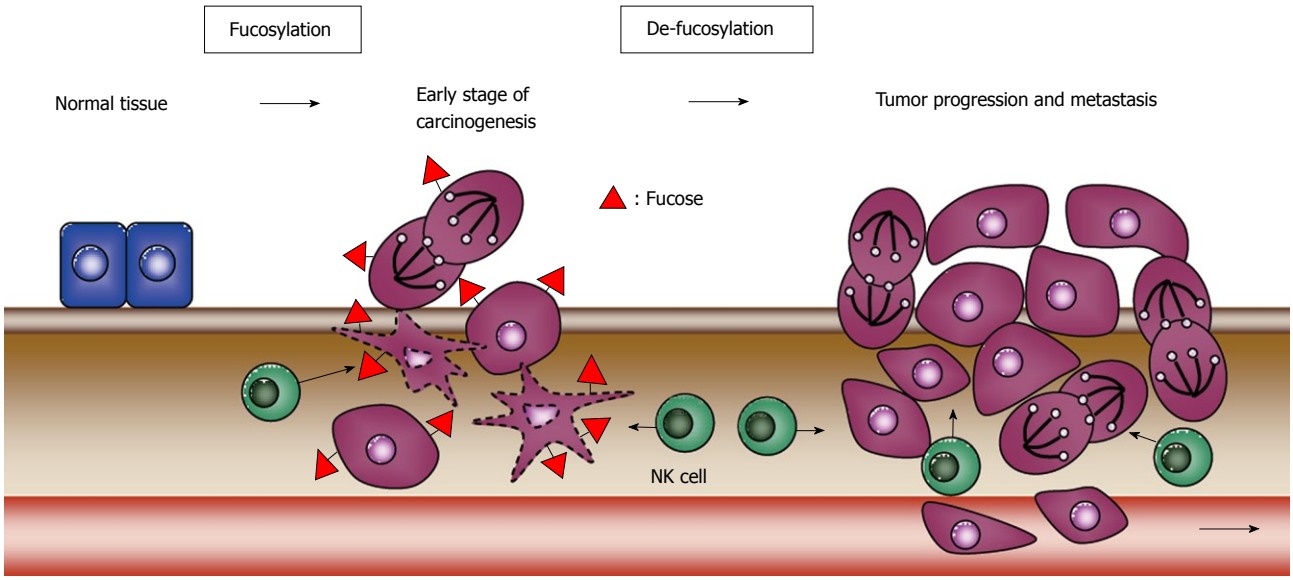

Figure 4 Schematic model of the biological function of fucosylation and de-fucosylation in modulating immune surveillance during colon carcinogenesis[109]. The level of fucosylation is not high in normal colon tissues, but is increased at an early stage in colon cancer. The cancer cells represented by the dotted line are apoptotic ones, which are attacked by NK cells. In certain types of advanced cancer, de-fucosylation through genetic mutation leads to escape from NK cell-mediated tumor surveillance and the acquisition of more malignant characteristics. These figures are modified from the data in reference 109.

in a wide variety of events in cancer biology, but only AFP-L3 and CA19-9 have been used for the diagnosis of cancer. In the case of cancer therapy, fucosylation has never been clinically applied so far. Our recent study indicates that modulation of fucosylation might be a promising target for cancer immune therapy. Recently identified fuocsylation-related tumor markers need to be validated using hundreds of clinical specimens. In addition, tumor markers are not only monitors for diagnosis or therapy, but also represent the biological characters of cancer cells. Thus, the mechanisms underlying the production of any tumor markers should be revealed. While we have investigated the biological significance of fucosylation in carcinogenesis and cancer progression, as described in this review, further analyses are required for its application to clinical tumor therapy. What molecules are the targets of fucosylation? Which linkages, α1-2, α1-3/4, α1-6, and/or *O*-fucose, are important? When is fucosylation up- or down-regulated during carcinogenesis and cancer progression? We would like to pose these questions to anyone studying cancer fucosylation. We believe that fucosylation is not just a tumor marker, but is also a possible factor determining the characteristics of cancer cells.

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CASE REPORT

Guillain-Barre syndrome associated with peginterferon alfa-2a for chronic hepatitis C: A case report

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Abstract

The recommended therapy for chronic hepatitis C (CHC) infection is the combination of a Pegylated interferon and Ribavirin. Almost all such patients on combination therapy experience one or more adverse events during the course of treatment. Significant neurological side effects are rare. A few cases of Bell's Palsy, chronic inflammatory demyelinating polyneuropathy and even one case of acute demyelinating polyneuropathy with atypical features for Guillain-Barre syndrome (GBS) associated with Interferon therapy have been reported but no report of GBS with typical features has been published. We present a case report of typical GBS associated with Peginterferon alfa-2a and Ribavirin used for treatment of CHC infection.

Key words: Guillain-Barre syndrome; Polyneuropathy; Acute demyelinating polyneuropathy; Pegylated interferon; Chronic hepatitis C

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INTRODUCTION

An estimated 170-180 million people worldwide are chronically infected with hepatitis C[1]. These patients are at increased risk of developing cirrhosis, hepatocellular carcinoma and hepatic decompensation. Chronic hepatitis C (CHC) is the leading cause of death from liver disease and the leading indication for liver transplantation in the US[2]. The number of deaths secondary to CHC is expected to rise[3]. The current standard therapy with Pegylated interferon in combination with Ribavirin is associated with significant side effects. Almost all patients treated with Peginterferon and Ribavirin experience one or more adverse events during the course of therapy. The most common are influenza-like symptoms (fatigue, headache, fever and rigors), psychiatric symptoms (depression, suicidal ideation, irritability, and insomnia) and bone marrow suppression. Less common are weight loss, hair loss, thyroid dysfunction, pulmonary toxicity, colitis, vision loss and hypersensitivity reaction[4,5]. Significant neurological side effects such as nerve palsy and peripheral neuropathy are rare[6]. A few cases of Bell's Palsy and chronic inflammatory demyelinating po-

Table 1 Time line showing the clinical course of the patient

Period 2008-09	Event	HCV RNA IU/mL	WBC $\times 10^3/\mu L$	ANC/μL	Hb g/dL	Platelets $\times 10^3/\mu L$	ALT IU/L	BT mg/dL	TSH IU/mL	IFN dose/wk	RBV dose/d
Early December	Start of HCV treatment	4 275 000	5.6	3600	15.9	NC[a]	66	0.7	1.55	180 mcg	1000 mg
Early January	Platelets decreased	309 230	5.0	2300	14.5	31	57	1.0	NA	135 mcg	No change
Late January	Start of neurological symptoms	18 880	3.9	1400	12.7	45	38	0.8	NA	Treatment held	
Mid February	Worsening of symptoms	NA	6.4	4000	15.1	61	59	0.6	1.92	Treatment on hold	
April	F/U visit[b] improvement in symptoms	499 660	7.2	4400	15.8	94	61	0.6	NA	Treatment on hold	

ANC: Absolute neutrophilic count; Hb: Hemoglobin; BT: Bilirubin total; IFN: Interferon; RBV: Ribavirin; F/U: follow-up; NA: Not available; NC: Not calculated. [a]Due to clumping of platelets, result was not recorded. Later on repeating, platelets were found to be 55 $\times 10^3/\mu L$; [b]Last follow up to hepatology clinic but patient is being followed up regularly by the neurologist in clinic and by hepatology staff.

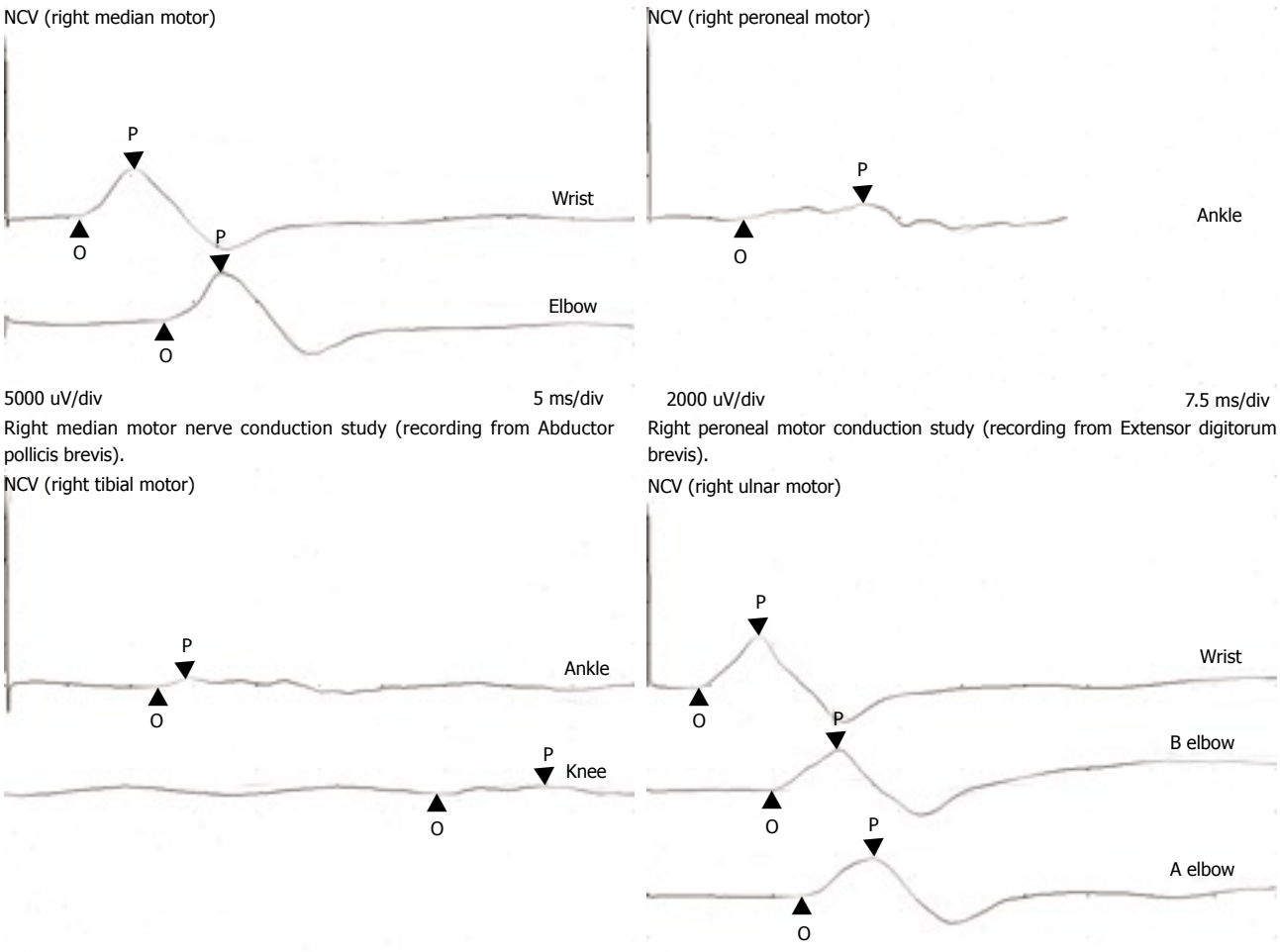
lyneuropathy (CIDP) and even one case of acute demyelinating polyneuropathy (AIDP) with atypical features for Guillain-Barre syndrome (GBS) associated with Interferon therapy have been reported, but no report of GBS with typical features has been published[5-9]. We present a case report of GBS that developed at wk 8 of therapy with Peginterferon alfa-2a.

CASE REPORT

A 55-year-old Caucasian male was referred to our center for treatment of CHC. The patient had a long-standing history of hepatitis C virus (HCV) infection, which was diagnosed 20 years earlier when he tried to donate blood. He was treatment naive. His risk factor for acquiring CHC was cocaine sniffing when he was young although he denied any intravenous drug use, unprofessionally made tattoos, body piercing or blood transfusions. The patient denied any history of jaundice, confusion or gastro intestinal bleeding. His only complaint was mild fatigue. A history of smoking (one pack per day) and social drinking was present. Family history revealed one brother with HCV infection. Physical examination showed no stigmata of advanced liver disease although the patient had grade 3 varices on EGD. The timeline of his clinical course is summarized in Table 1.

Initial laboratory findings before initiating the HCV treatment included, Aspartate Transaminase of 60 (0-40) IU/L, Alanine Transaminase of 62 (0-55) IU/L, total bilirubin 0.6 mg/dL, albumin 3.8 g/dL, and International Normalized Ratio was 1.0. Anti smooth muscle, antimicrosomal, anti alpha-one antitrypsin and antineutrophilic antibodies were normal. Hepatitis B virus serology was negative and iron studies were normal. The patient's HCV RNA viral load was 1 352 000 IU/mL. His genotype was 1a. Liver biopsy revealed stage 3 bridging fibrosis with mild macro vesicular steatosis and severe inflammation. The patient was started on Pegylated interferon alfa-2a 180 mcg/mL subcutaneously per week and Ribavirin 1000 mg/d in divided doses. Because of thrombocytopenia, the interferon dose was decreased to 135 mcg/mL weekly. He responded to the treatment with a more than 2 $\log_{10}$ drop in HCV RNA at wk 8. At that time, he visited a local hospital complaining of numbness of the face, difficulty eating, loss of taste sensation and facial diplegia. The work up for stroke was negative and magnetic resonance imaging (MRI) of the brain was normal. He was seen by a neurologist, who made the diagnosis of Bell's Palsy and started the patient on oral steroids. Peginterferon was discontinued at that time, and the patient was advised to follow up with the neurologist.

Subsequently, the patient developed back pain, progressive weakness and neuropathic pain in both lower extremities, leading to difficulty in ambulation. Computerized tomography scans and MRI of the lumbar and thoracic spine were normal. These symptoms progressed over two weeks and the patient became wheelchair bound. He was then admitted to a local hospital where physical examination revealed bilateral weakness involving both upper and lower facial muscles, normal muscle strength in upper extremities but decreased in the lower extremities. There were decreased deep tendon reflexes (DTRs) in both upper extremities, absent DTRs at the knees bilaterally and at the right ankle and decreased at the left ankle. The patient underwent an electromyography study (EMG), nerve conduction study and lumbar puncture for cerebrospinal fluid (CSF) analysis. EMG and nerve conduction studies (Figure 1 and Tables 2, 3) showed that the right radial sensory distal latency was prolonged (2.8 ms; normal < 2.6 ms) with a diminished amplitude response (11 uV; normal > 20 uV) and the right sural sensory response was absent (technically difficult). The right median motor distal latency was markedly prolonged (6 ms; normal < 4.4 ms) with a slow conduction velocity (37 m/s; normal > 49 m/s) and prolonged F-wave latency (33 ms; normal < 31 ms). The right ulnar motor distal latency was prolonged (4.1 mV; normal < 3.5 ms); the conduction velocity was slowed both in the forearm



Right median motor nerve conduction study (recording from Abductor pollicis brevis).

Right peroneal motor conduction study (recording from Extensor digitorum brevis).

Right tibial motor conduction study (recording from Abductor hallucis brevis).

Right ulnar motor conduction study (recording from Abductor digiti minimi).

The waveforms correspond with the data in the table below:

Site	NR	Onset (ms)	Norm onset (ms)	O-P Amp (mV)	Norm O-P Amp	Site 1	Site 2	Delta-0 (ms)	D (cm)	Velocity (D/Delta) (m/s)	Norm velocity (m/s)
Right median motor (Abductor pollicis brevis)											
Wrist		6.0	< 4.2	5.6	> 4.4	Elbow	Wrist	6.7	25	37	> 49
Elbow		12.7		5.6							
Right peroneal motor (Extensor digitorum brevis)											
Ankle		11.4	< 5.7	0.7	> 2.2						
Below fibular	NR										
Right tibial motor (Abductor hallucis brevis)											
Ankle		12.1	< 5.7	1.0	> 2.8	Knee	Ankle	22.3	43	19	> 41
Knee		34.4		0.9							
Right ulnar motor (Abductor digiti minimi)											
Wrist		4.1	< 3.5	6.1	> 5.6	B elbow	Wrist	5.9	24	41	> 49
Below elbow		10.0		4.8		A elbow	B elbow	2.3	11	48	> 49
Above elbow		12.3		4.4							

NR: No response; Norm: Normal; O-P: Onset-Peak; Amp: Amplitude; Vel: Velocity; D: Distance; A: Above; B: Below.

Figure 1 Electromyography/nerve conduction studies.

segment and across the elbow whilst the F-wave was normal. The right peroneal motor distal latency was markedly prolonged with a low amplitude dispersed response and absent proximal response. The right tibial motor distal latency was markedly prolonged with a low amplitude dispersed waveform and slow conduction velocity. Concentric needle examination of selected distal right lower extremity muscles demonstrated a reduced number of voluntary motor units in right tibialis anterior without any spontaneous activity or motor unit changes. The CSF analysis revealed markedly elevated protein levels of 405.8 mg/dL, (normal: 15.0-45.0 mg/

Table 2 Electromyography studies

Side	Muscle	Nerve	Root	Insertional activity	Fibrillations	Psw	Amp	Dur	Poly	Interphase pattern
Right	MedGastroc	Tibial	S1-2	Nml	Nml	Nml	Nml	Nml	0	Nml
Right	AntTibialis	Deep br peroneal	L4-5	Nml	Nml	Nml	Nml	Nml	0	25%

Nml: Normal; Psw: Positive sharp waves; Amp: Amplitude; Dur: Duration; Poly: Polyphase activity. Electrical activity of the muscles at rest (Insertional activity, Fibrillations, Psw) and with voluntary activation (Amp, Dur, Poly, Interphase) showing that most of the results were normal, reflecting that patient had an acute event of neurological symptoms and did not have a chronic ongoing muscle disease.

Table 3 Nerve conduction studies

	Distal latency (m/s)	Conduction velocity (m/s)	Amplitude sensory (uV) motor (mV)
Sensory			
Right radial	2.8 (NML < 2.6)		11 (NML > 20)
Right sural	Absent[a]		Absent[a]
Motor			
Right median	6.0 (NML < 4.4)	37 (NML > 49)	5.6 (NML > 4.2)
Right ulnar	4.1 (NML < 3.5)	41 (NML > 49)	6.0 (NML > 5.6)
Right peroneal	11.4 (NML < 5.7)		0.7 (NML > 2.2)
Right tibial	12.1 (NML < 5.7)		1.0 (NML > 2.8)
F wave			
Right median	33 (NML < 31)		
Right ulnar	27.6 (NML < 31)		
Right peroneal	Absent		
Right tibial	Absent		

[a]Technically difficult; NML: Normal.

dL), normal glucose level of 67 mg/dL (normal: 40-70 mg/dL), 3 white blood cell (WBC)/μL and 3 red blood cell/uL. Based upon these clinical and laboratory findings, the patient was diagnosed with AIDP (GBS) and was started on intravenous immunoglobulins (IVIG). Other laboratory tests included normal complete blood count, blood chemistry (chemistry-8 panel), thyroid stimulating hormone, normal CSF Lymes antibodies and normal CSF immunoglobulin A level. Thereafter, the patient was transferred to a rehabilitation center.

As per the last follow up at the hepatology clinic, the patient was able to walk short distances with a walker, with left sided facial strength improvement and right sided weakness. However, as per the latest follow up visit to the neurology clinic, he does not even require a walker. The patient still shows some neurological deficit although he is back at work. The neuropathic pain has improved significantly and the patient demonstrates improved muscle strength. Interferon therapy is still on hold.

DISCUSSION

GBS is a heterogeneous condition with several variant forms. It is an acute monophasic progressive disease presenting with symmetric muscle weakness and absent or decreased deep tendon reflexes[10].

Pathophysiology and causes

An immune response to a preceding infection that can cross-react with peripheral nerve components is the proposed mechanism of GBS. This immune response can be directed against the myelin or the axon of the peripheral nerve, resulting in demyelinating and axonal forms of GBS. Campylobacter Jejuni infection is the most commonly identified precipitant of GBS[11] although our patient did not have any gastrointestinal symptoms making, C Jejuni highly unlikely. Other infections such as Haemophilus influenzae, Mycoplasma pneumoniae and Cytomegalovirus are the most commonly identified precipitant of GBS. However, our patient did not show any evidence of flu-like symptoms or systemic signs and symptoms of infection and there was no evidence of pneumonia on chest x-ray[12]. CSF pleocytosis is common in patients who have GBS and concurrent HIV infection[13] but our patient had only 3 WBCs. Certain vaccinations such as Influenza vaccination[14] and Meningococcal vaccination have also been associated with GBS but our patient did not receive any of these vaccines. Industrial toxins and drugs can also cause demyelinating neuropathies. Our patient had no exposure to any of toxins or drugs other than Pegylated interferon alpha 2-a and Ribavirin.

Diagnosis

The typical findings with lumbar puncture in patients with GBS are an elevated CSF protein with a normal WBC count. AIDP is the most common form of GBS in the United States and Europe, representing approximately 85 to 90 percent of cases. Clinical neurophysiology studies (i.e. electromyography and nerve conduction studies) show evidence of an AIDP. The earliest abnormalities seen on clinical neurophysiology studies in patients with AIDP are prolonged or absent F waves, reflecting demyelination at the level of the nerve roots[10,15]. Sensory nerve conduction studies reveal absent responses or slowed conduction velocities. Typically, the sural sensory response is normal, while median and ulnar sensory responses are affected (sural sparing).

Treatment

Treatment of GBS according to the American Academy of Neurology recommendation[16] is with plasma exchange or IVIG. Both hasten recovery from GBS. The beneficial effects of plasma exchange and IVIG are equivalent. Steroid treatment alone is not beneficial. Plasma exchange is recommended for nonambulatory adult patients with GBS who start treatment within

four weeks of the onset of neuropathic symptoms or for ambulatory patients who start treatment within two weeks of the onset of neuropathic symptoms. IVIG is recommended for nonambulatory adult patients with GBS who start treatment within two or possibly four weeks of the onset of neuropathic symptoms. Overall, about 80 percent of patients with GBS either recover completely or are left with only minor deficits which do not interfere with activities of daily living.

Neurological side effects of interferon are rare. However, a variety of peripheral neuropathies have been reported such as Bell's palsy, optic neuropathy, sensory and autonomic neuropathy, CIDP and more recently AIDP (atypical GBS)[6-9,11]. We did not test for IFN antibodies (that could possibly cross-react), did not rule out all the GBS related infectious causes definitely and did not check autoimmune markers at the time of onset of neurological symptoms. However, our patient did not have any clinical signs of any other autoimmune disorder. This is the second reported case of AIDP and the first case of typical GBS that was associated with treatment for chronic hepatitis C with Pegylated interferon alpha 2. Although a few cases of Bell's palsy have been reported with HCV therapy[6], only one atypical GBS has been reported after 16 wk of HCV treatment[7]. Our case is unique in the way our patient first developed Bell's palsy, and was then subsequently diagnosed with GBS. Unlike the prior atypical GBS reported, our patient had all the required cardinal features of GBS. Another notable observation is that these findings were reported within only 8 wk of initiation of treatment.

We think it is important for clinicians, and in particular hepatologists to keep this association with GBS in mind when prescribing Peginterferon alfa-2a for HCV treatment. Close attention should be paid to any neurological symptoms developing during the course of treatment. Prompt referral to a neurologist is warranted if these symptoms develop. In addition, patients should have a close and regular follow up with the Hepatologist where the treatment was initiated.

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CASE REPORT

Liver failure after an uncovered TIPS procedure associated with hepatic infarction

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Abstract

Transjugular intrahepatic portosystemic shunt (TIPS) is a safe and effective procedure for the treatment of complications of liver cirrhosis, such as refractory ascites, hepatic hydrothorax and refractory variceal bleeding. The aim of this paper is to describe a rare case of liver failure after a TIPS procedure. A 38-year-old diabetic male with Child-Pugh C liver cirrhosis due to chronic hepatitis C infection who had developed refractory ascites was scheduled for a TIPS procedure. Within 24 h following TIPS placement, the patient developed distributive shock, jaundice, persistentgrade 3 hepatic encephalopathy, severe coagulopathy and acute renal failure. He was treated with lactulose enemas, broad-spectrum antibiotics and blood-derived products. Laboratory data revealed a 100-fold increase in aminotransferases and a non-enhanced computed tomography showed an irregular hypodense area in the right posterior segment of the liver. Despite being initially being in a stable condition, the patient developed progressive liver failure and died 2 mo later. Hepatic infarction is an uncommon phenomenon after a TIPS procedure; however, it can greatly complicate the course of a disease in a patient with an already compromised liver function.

Key words: Hepatic ischemia; Ischemic hepatitis; Liver infarction; Transjugular intrahepatic portosystemic shunt; Complications

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INTRODUCTION

Transjugular intrahepatic portosystemic shunts (TIPS) have become a valuable tool in the management of cirrhotic patients[1]. TIPS are frequently employed in the treatment of refractory variceal bleeding, refractory ascites, the Budd-Chiari syndrome, and hepatic hydrothorax and hepatorenal syndromes[2]. TIPS reduce portal pressure by creating a connection between a

suprahepatic vein and an intrahepatic branch of the portal vein through a minimally invasive approach. These shunts can be placed by a skilled gastroenterologist or interventional radiologist. The mortality rate is around 1%-2%[3].

The major complications of TIPS are stent dysfunction and hepatic encephalopathy[4]. Stent dysfunction has been significantly reduced with the use of polytetrafluoroethylene (PTFE)-covered stents, with low reintervention rates[5,6]. Hepatic encephalopathy and other less frequent complications of TIPS remain a concern and are subjects for future research, as the number of procedures performed worldwide increases. The aim of this report is to describe a rare case of liver failure after a TIPS procedure.

CASE REPORT

A 38-year-old male with a history of hypergonadotrophic hypogonadism due to bilateral testicular atrophy after cryptorchidism, and type 2 diabetes mellitus treated with insulin, developed thrombocytopenia. A diagnostic work-up for the hematological cytopenia revealed portal hypertension due to a chronic hepatitis C virus infection.

He had experienced variceal bleeding which was treated with band ligation and portal hypertensive colopathy, treated with argon plasma. One year prior to admission he developed refractory ascites which was treated with evacuatory paracentesis every two weeks. A TIPS procedure was proposed for the treatment of refractory ascites and a comprehensive work-up was performed. A transthoracic echocardiogram showed normal right and left cardiac function without evidence of pulmonary hypertension. A critical flicker test revealed minimal hepatic encephalopathy, which was managed with oral L-ornithine-L-aspartate.

Serum alpha fetoprotein was normal. The portal vein was patent and no focal hepatic lesions were identified on ultrasound evaluation.

Prior to the TIPS procedure, the Model for End-stage Liver Disease score was 6. Physical examination showed tension ascites with no signs of hepatic encephalopathy. Laboratory data at admission (d 0) and follow-up are shown in Table 1. After an evacuatory paracentesis, the patient underwent a TIPS procedure, shunting the right portal vein to the right suprahepatic vein using a 10 mm, 6 cm long uncovered stent (Figure 1). An uncovered stent was placed due to the patient's poor income.

Within 24 h of the procedure, the patient developed fever (38.7℃), tachycardia, hypotension, grade 1-2 hepatic encephalopathy, jaundice, left-shifted leucocytosis and acute renal failure; alanine aminotransferase increased up to 1 209 UI/L and aspartate aminotransferase to 3 128 UI/L, with worsening hyperbilirubinemia and coagulopathy. Blood and ascites cultures were taken and supportive therapy was begun.This included dosing the patient with broad-spectrum antibiotics (imipenem, vancomycin and amikacin adjusted to renal function),

Table 1 Laboratory data during the seven days of hospital management

Lab/Day	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Hemoglobin	10	11.6	8.4	7	8.1	7.4	7.5
WBC	3.8	13.5	5.6	3.9	2.2	1.9	1.8
Platelets	40	83	41	25	18	22	26
Creatinine	0.7	1.1	1.0	1.1	0.8	0.8	0.7
Bilirubin	1.2	5.4	5.6	4.1	4	4.3	3.9
ALT	25	1209	816	567	389	212	153
AST	37	3128	1110	467	282	145	74
INR	1.2	2.2	3.1	2.1	1.5	2.1	2.0
Albumin	2.7	1.8	1.7	1.9	2.3	2.2	2.3
HE	0	3	2	2	2	2	1-2
Troponin I	-	0	0	-	-	-	-
CK/CK-MB	-	30/11	28/11	-	-	-	-
TPT	-	-	40	38.8	-	-	-
Fibrinogen	-	-	94	200.8	-	-	-
D-dimer	-	-	203	363.4	-	-	-
MELD	6	23	26	21	14	18	16

Abbreviations: Definition-units: Hemoglobin-gr/dL; WBC: White blood cell count-cell/cc; Platelets-cell/cc; Creatinine-mg/dL; Bilirubin-mg/dL; ALT: Alanine aminotransferase-UI/L; AST: Aspartate aminotransferase-UI/L; INR: International normalized ratio-arbitrary units; Albumin-gr/dL; HE: Hepatic encephalopathy-West Haven criteria; Troponin I-UI/L; CK/CK-MB: Creatine kinase/subunit-MB-UI/L; TPT: Thromboplastin time-seconds; Fibrinogen-μg/dL; D-dimer-UI/L; MELD: Model for end-stage liver disease.

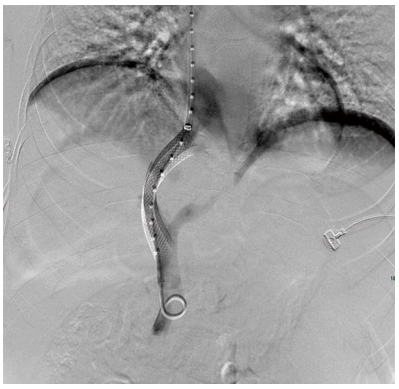

Figure 1 Uncovered TIPS placed through the right suprahepatic vein to the right portal vein.

rectal lactulose, and vasopressor treatment with norepinephrine lasting 36 h. Antibiotics were suspended on the fifth day due to the absence of clinical, radiological or microbiological evidence of infection. Liver failure was identified as the cause of distributive shock. After discontinuing the antibiotics, the patient did not exhibit any further worsening of his general condition, and no fever or leukocytosis were documented.

However, during the next 48 h, the patient's condition worsened. He developed lower gastrointestinal bleeding which was attributed to portal colopathy, with a hemoglobin drop from 11.6 to 7 gr/dL and disseminated intravascular coagulation (DIC), which was treated with an infusion of fresh frozen plasma and cryoprecipitates. A Doppler ultrasound showed a patent TIPS and normal flow in main hepatic artery. An abdominal Computed Tomography scan showed abundant ascites and a hypodense triangular-shaped heterogeneous area in segment 5 of the liver, suggestive of hepatic infarc-

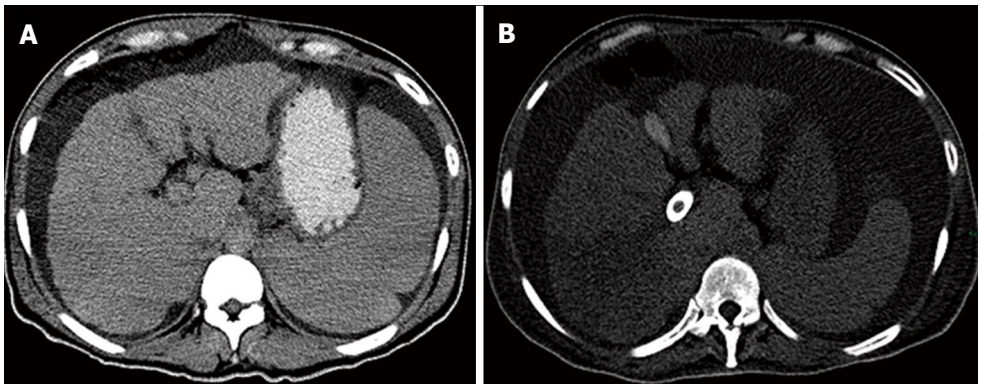

Figure 2 Abdominal computed tomography evaluation. A: Abdominal CT scan one year prior to TIPS placement showing a small nodular liver with ascites and splenomegaly; B: Abdominal CT scan one day after TIPS placement showing a hypodense triangular-shaped heterogeneous area in the right posterior segments of the liver, suggestive of hepatic ischemia; note how the spleen size is significantly reduced.

tion (Figure 2). No clinical signs of heart failure or electrocardiographic changes were identified. Cardiac enzymes were within normal limits and a new transthoracic echocardiogram showed left ventricle hyperkinesia with normal ejection fraction and no signs of pulmonary hypertension.

After 7 d of supportive therapy the patient's condition improved; liver enzymes, bilirubin, international normalized ratio and blood cell count all improved, but none returned to baseline. He was discharged with a close follow-up. The patient developed progressive liver failure and died 2 mo later.

DISCUSSION

TIPS provide rapid decompression of portal pressure by creating a shunt, from a high-pressure portal vein branch to a low-pressure hepatic vein through the hepatic parenchyma. During the last two decades, TIPS have revolutionized the field of portal hypertension management. Inserting PTFE-covered stents has resulted in low thrombosis and stenosis rates, a technological breakthrough that, in turn, has reduced reintervention rates. Because of the low morbidity and mortality rates associated with it, a TIPS procedure now often constitutes a therapeutic bridge to liver transplantation for an increasing number of patients unfit for a surgical derivation procedure.

The hyperdynamic circulation state that characterizes liver cirrhosis induces an increase in hepatic blood flow in these patients, leading to a total hepatic perfusion 25% higher than healthypatients, but portosystemic intrahepatic shunts and sinusoidal capillarization reduce the amount of blood flow in contact with the sinusoidal membrane (functional hepatic flow), leading to a 60% lower sinusoidal perfusion in cirrhotic patients, compared with 95% in healthy patients[7-10].

Hepatic ischemia is a rare event after a TIPS procedure, with fewer than 10 cases described in the literature. The first case reported was an asymptomatic hepatic infarction identified incidentally by nuclear imaging and confirmed by angiography[11]. Other cases of hepatic ischemia have been related to hepatic arterial injury by occlusion or placement of TIPS in the artery and an arterio-venous fistula treated with embolization with subsequent infarction[12-14]. Two cases of liver failure associated with hepatic infarction after a TIPS procedure have been reported[15,16].

The pathogenesis of hepatic infarction after a TIPS procedure is not clear. The stolen portal flow to the hepatic veins via TIPS could compromise hepatic perfusion in the involved segments; however, in order to perpetuate infarction in such a localized manner, arterial flow could also be disturbed. Several hypotheses have been proposed, such as direct arterial injury, decreased hepatic arterial flow due to hypotension and shock, and occult hepatic artery thrombosis due to DIC[15]. An alternative hypothesis that could explain this complication following TIPS is the extrinsic compression of a branch of the hepatic artery after the deployment of the stent in the parenchyma. Histological studies have shown that this compression is usually minimal[17], however, those patients with a higher degree of compression might be those who ultimately develop infarction.

On the other hand, it has been argued that the pathophysiology of hepatic infarction after TIPS is a "partial" Budd-Chiari syndrome, in which the PTFE-covered part of the stents produces hepatic congestion by obstructing a part of the hepatic vein, suggesting that puncturing the hepatic vein near its ostium, would avoid occlusion of the hepatic flow[18]. Nevertheless, neither the occlusion of the hepatic vein has been constantly associated with hepatic infarction nor has this approach ever been proven useful to prevent it[16]. Furthermore, the current case developed it in spite of using uncovered TIPS.

In conclusion, hepatic infarction following a TIPS procedure is a rare but potentially devastating complication. Avoidance of any injury to the hepatic artery during the procedure, ensuring an adequate postoperative hepatic perfusion as well as aggressive therapeutic treatment of early complications are mandatory. Patients with Child-Pugh C cirrhosis should be monitored closely so that potentially fatal liver failure may be overcome.

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Meetings

Events Calendar 2010

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

October 23-27
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Instructions to authors

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Acknowledgments

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J Gastroenterol 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

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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/eid.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).

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