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ORIGINAL ARTICLE

Is an estimated glomerular filtration rate better than creatinine to be incorporated into the end-stage liver disease score?

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Abstract

AIM: To incorporate estimated glomerular filtration rate (eGFR) into the model for end-stage liver disease (MELD) score to evaluate the predictive value.

METHODS: From January 2004 to October 2008, the records of 4127 admitted cirrhotic patients were reviewed. Patients who survived and were followed up as outpatients were defined as survivors and their most recent available laboratory data were collected. Patients whose records indicated death at any time during the hospital stay were defined as non-survivors (in-hospital mortality). Patients with incomplete data or with cirrhosis due to a congenital abnormality such as primary biliary cirrhosis were excluded; thus, a total of 3857 patients were enrolled in the present study. The eGFR, which was calculated by using either the modification of diet in renal disease (MDRD) equation or the chronic kidney disease epidemiology collaboration (CKD-EPI) equation, was incorporated into the MELD score after adjustment with the original MELD equation by logistic regression analysis [bilirubin and international normalized ratio (INR) were set at 1.0 for values less than 1.0].

RESULTS: Patients defined as survivors were significantly younger, had a lower incidence of hepatoma, lower Child-Pugh and MELD scores, and better renal function. The underlying causes of cirrhosis were very different from those in Western countries. In Taiwan, most cirrhotic patients were associated with the hepatitis virus, especially hepatitis B. There were 16 parameters included in univariate logistic regression analysis to predict in-hospital mortality and those with significant predicting values were included in further multivariate analysis. Both 4-variable MDRD eGFR and 6-variable MDRD eGFR, rather than creatinine, were significant predictors of in-hospital mortality. Three new equations were constructed (MELD-MDRD-4, MELD-MDRD-6, MELD-CKD-EPI). As expected, original MELD score was a significant predictor of in-hospital mortality (odds ratio = 1.25, $P < 0.001$). MELD-MDRD-4 excluded serum creatinine, with the coefficients refit among the remaining 3 variables, i.e., total bilirubin, INR and 4-variable MDRD eGFR. This model represented an exacerbated outcome over MELD score, as suggested by a decrease in chi-square (2161.45 *vs* 2198.32) and an increase in -2 log (likelihood) (2810.77 *vs* 2773.90). MELD-MDRD-6 included 6-variable MDRD eGFR as one of the variables and showed an improvement over MELD score, as suggested by an increase in chi-square (2293.82 *vs* 2198.32) and a decrease in -2 log (likelihood) (2810.77 *vs* 2664.79). Finally, when serum creatinine was replaced by CKD-EPI eGFR, it showed a slight improvement compared to the original

MELD score (chi-square: 2199.16, -2 log (likelihood): 2773.07). In the receiver-operating characteristic curve, the MELD-MDRD-6 score showed a marginal improvement in area under the curve (0.909 *vs* 0.902), sensitivity (0.854 *vs* 0.819) and specificity (0.818 *vs* 0.839) compared to the original MELD equation. In patients with a different eGFR, the MELD-MDRD-6 equation showed a better predictive value in patients with eGFR $\geqslant$ 90, 60-89, 30-59 and 15-29.

CONCLUSION: Incorporating eGFR obtained by the 6-variable MDRD equation into the MELD score showed an equal predictive performance in in-hospital mortality compared to a creatinine-based MELD score.

Key words: Liver cirrhosis; Estimated glomerular filtration rate; End-stage liver disease; Modification of diet in renal disease; Renal function

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INTRODUCTION

For over 30 years, the Child-Pugh score, which is based on 5 variables (ascites, encephalopathy, serum total bilirubin, serum albumin and prothrombin time), has been the main prognostic tool and has proved to be a robust prognostic predictor in different situations[1]. However, the value of this score is limited due to subjective interpretation of ascites and encephalopathy and an inappropriate classification of serum bilirubin. Increasing evidence in the literature suggests that the development of acute kidney injury is an ominous and common event in cirrhotic patients[2]. Therefore, routine serum creatinine tests have been found to significantly improve the prognostic accuracy of the Child-Pugh score and serum creatinine is an independent predictor of survival in cirrhotic patients[3]. In fact, renal function is 1 of the 3 variables [serum bilirubin, international normalized ratio (INR) and serum creatinine] in the model for end-stage liver disease (MELD) score, which is a good predictor for assessing 3 mo mortality and is currently used to determine priority for orthotopic liver transplantation[1,4,5].

Unlike the Child-Pugh score, the 3 variables of the MELD score are selected on the basis of statistical analysis and not empirical analysis. Even although serum creatinine has a strong prognostic value in cirrhotic patients, it is considered an insensitive predictor in such patients because of the patient's reduced muscle mass; this may lead to an overestimation of creatinine clearance compared to inulin clearance[1,6,7]. Thus, serum creatinine is not a very accurate gauge, especially in detecting early loss of renal function in cirrhotic patients[1,6,8], and there are approximately 15% to 20% of patients whose survival cannot be accurately predicted by the MELD score[6,9].

Recently, Lim *et al*[10] suggested that there was a significant association between measured glomerular filtration rate (GFR) and survival after adjustment for MELD; however, estimated GFR (eGFR) calculated by the modification of diet in renal disease (MDRD) equation was only moderately correlated with measured GFR in cirrhotic patients[10]. The creatinine-based MDRD equation is widely used in the general population for calculating GFR and is considered a gold standard in nephrology[8,11]. It is also the best formula for the detection of moderate renal dysfunction in advanced liver disease[12,13]. Nowadays, most publications that mention the eGFR of cirrhotic patients have been using databases from liver transplant registries. The aim of the present study was to evaluate the difference between eGFR obtained either by MDRD or by the new creatinine-based equation, known as the chronic kidney disease epidemiology collaboration (CKD-EPI) formula[14], when eGFR was incorporated into the MELD score to predict in-hospital mortality in a broad population of cirrhotic patients.

MATERIALS AND METHODS

Ethics

This work was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association and the institutional review board.

We performed a retrospective, cross-sectional study on Taiwanese cirrhotic patients in the Mackay Memorial Hospital. Mackay Memorial Hospital is a tertiary referral center for liver disease. This study is a single center investigation and all patients of the study were afferent, directly diagnosed and followed-up in Mackay Memorial Hospital.

Patient information and data collection

The design of this single-center study was retrospective and cross-sectional and the protocol was approved by the local ethics committee. Patients diagnosed with cirrhosis were selected from those admitted to Mackay Memorial Hospital between January 2004 and October 2008.

The records of 4127 cirrhotic patients from a total of 228 345 admitted patients were reviewed. Patients who survived and were followed up as outpatients were defined as survivors and their most recent available laboratory data were collected. Patients whose records indicated death at any time during the hospital stay were defined as non-survivors (cases of in-hospital mortality) and laboratory data for these patients comprised the data collected during their admission. In the case of patients with multiple admissions, the records before those of the last admission were excluded. Demographic data,

Child-Pugh scores and information regarding underlying comorbidities were obtained from the most recent laboratory examinations. Patients with incomplete data or with cirrhosis due to congenital abnormality such as primary biliary cirrhosis were excluded; thus, a total of 3857 patients were enrolled in the present study. None of these patients had received liver transplants.

Equations for estimated GFR

The eGFR was calculated according to the formula below:

MDRD-4[11] = 175 × $(Scr)^{-1.154}$ × $(age)^{-0.203}$ × (0.742 if female) × (1.178 if black),

MDRD-6[11] = 170 × $(Scr)^{-0.999}$ × $(age)^{-0.176}$ × (0.762 if female) × (1.180 if black) × $(SUN)^{-0.170}$ × $(albumin)^{0.318}$,

CKD-EPI[14] = 141 × min $(Scr/\kappa, 1)^{\alpha}$ × max $(Scr/\kappa, 1)^{-1.209}$ × 0.993^{age} × (1.018 if female) × (1.159 if black),

where MDRD-4 is 4-variable MDRD, MDRD-6 is 6-variable MDRD, age is given in years, albumin in g/dL, Scr is serum creatinine (mg/dL), SUN is serum urea nitrogen concentration (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of serum creatinine/κ or 1.

Statistical analysis

Continuous variables were summarized as mean ± SD unless otherwise stated. We initially compared the demographic data and laboratory variables of survivors and non-survivors using Student's *t* test and χ^2 test. To formally examine the relationship among different means of eGFR and MELD as predictors of in-hospital mortality, several multivariate models were constructed. MELD score was calculated according to the original description: MELD = 11.2 LN (INR) + 3.78 LN (bilirubin) + 9.57 LN (creatinine) + 6.43[15].

After adjustment with the original MELD equation by logistic regression analysis (bilirubin and INR were set at 1.0 for values less than 1.0), new MELD equations which incorporate eGFR to replace serum creatinine were constructed and listed below:

MELD-MDRD-4 = 8.82 LN (INR) + 4.07 LN (bilirubin) + (-5.13) LN [eGFR (MDRD-4)] + 30.57,

MELD-MDRD-6 = 8.78 LN (INR) + 383 LN (bilirubin) + (-5.14) LN [eGFR (MDRD-6)] + 30.05,

MELD-CKD-EPI = 8.80 LN (INR) + 4.01 LN (bilirubin) + (-5.37) LN [eGFR (CKD-EPI)] + 31.93.

The new MELD equations were rounded to the nearest integer for easy use. Unlike the original MELD equation, there was no preinstall upper limit in these new equations.

Logistic regression analysis were conducted for investigating the odds ratios (OR) of predicting in-hospital mortality by different models, different new MELD equations, and MELD equations in patients with different eGFR levels. The difference in different MELD equations in predicting in-hospital mortality was investigated by logistic regression analysis. The results of these analyses were used to construct a receiver-operating characteristic (ROC) curve from which we sought the optimum cutoff point for predicting successful sites. The optimum cutoff point was defined as the point on the ROC curve closest to the point (0, 1), where the false-positive rate was zero and the sensitivity was 100%. The area under the curve and 95% CI were calculated. A *P* value of less than 0.05 was considered statistically significant. All statistical analysis were performed using SPSS software (version 17.0, SPSS Inc., Chicago, IL, United States).

RESULTS

Patient characteristics

Table 1 presents the clinical characteristics, demographic data and laboratory data of the study subjects. Patients defined as survivors were significantly younger, had a lower incidence of hepatoma, lower Child-Pugh and MELD scores, and better renal function. The underlying causes of cirrhosis were very different from those in Western countries. In Taiwan, most cirrhotic patients were associated with the hepatitis virus, especially hepatitis B. Diagnoses such as non-alcoholic steatohepatitis or cholestatic liver disease were seldom confirmed and were classified as unknown.

Relationship between estimated GFR, total bilirubin, INR and MELD score as a predictor of in-hospital mortality

There were 16 parameters included in univariate logistic regression analysis to predict in-hospital mortality. Those with a significant predicting value are listed in Table 2 and were further evaluated by multivariate logistic regression analysis. Both eGFR (MDRD-4) and eGFR (MDRD-6), rather than creatinine, were significant predictors of in-hospital mortality.

Table 3 shows several multivariate models for the prediction of in-hospital mortality. As expected, model 1, containing the MELD score only, was a significant predictor of in-hospital mortality (OR = 1.25, $P < 0.001$). Model 2 excluded serum creatinine, with the coefficients refit among the remaining 3 variables, i.e., total bilirubin, INR and eGFR (MDRD-4). This model represented an exacerbated outcome over model 1, as suggested by a decrease in χ^2 (2161.45 *vs* 2198.32) and an increase in -2 log (likelihood) (2810.77 *vs* 2773.90). Model 3 included eGFR (MDRD-6) as one of the variables and showed an improvement over model l, as suggested by an increase in chi-square (2293.82 *vs* 2198.32) and a decrease in -2 log (likelihood) (2810.77 *vs* 2664.79). Finally, when serum creatinine was replaced by eGFR (CKD-EPI), it showed a slight improvement compared to model 1 [χ^2: 2199.16, -2 log (likelihood): 2773.07].

Incorporation of estimated GFR into the MELD score to replace serum creatinine

The efficacy of new MELD equations for the prediction of in-hospital mortality is listed in Table 4. Compared to the original MELD equation, only MELD-MDRD-6 showed a better predictive value, as suggested by an in-

Table 1 Clinical characteristics, demographic data and laboratory data of 3857 cirrhotic patients

Parameter	All patients (n = 3857)	Survivors (n = 2375)	Non-survivors (n = 1482)	P value
Age, yr	60.73 ± 14.05	59.02 ± 14.02	63.48 ± 13.65	< 0.001
Male, n (%)	2665 (69.1)	1651 (69.52)	1014 (68.42)	NS (0.474)
Hepatoma, n (%)	1385 (35.9)	653 (27.5)	732 (49.4)	< 0.001
Cause of liver cirrhosis, n (%)				< 0.001
Hepatitis C	930 (24.1)	568 (23.9)	362 (24.4)	-
Hepatitis B	1090 (28.3)	631 (26.6)	459 (31)	-
Alcoholic	813 (21.1)	580 (24.4)	233 (15.7)	-
Hepatitis C + hepatitis B	106 (2.7)	70 (2.9)	36 (2.4)	-
Hepatitis C + alcohol	60 (1.6)	39 (1.6)	21 (1.4)	-
Hepatitis B + alcohol	191 (5)	127 (5.3)	64 (4.3)	-
Hepatitis C + hepatitis B + alcohol	33 (0.9)	19 (0.8)	14 (0.9)	-
Not hepatitis C, hepatitis B or alcohol	634 (16.4)	341 (14.4)	293 (19.8)	-
Ascites, n (%)	1861 (48.2)	825 (34.7)	1036 (69.9)	< 0.001
Hepatic encephalopathy, n (%)	1097 (28.4)	434 (18.3)	663 (44.7)	< 0.001
Child–Pugh points	8.36 ± 2.57	7.11 ± 1.97	10.37 ± 2.1	< 0.001
MELD score	18.9 ± 10.26	13.15 ± 5.57	27.98 ± 9.36	< 0.001
Albumin, 3.5-5 g/dL	2.95 ± 0.73	3.24 ± 0.68	2.49 ± 0.55	< 0.001
Total bilirubin, 0.3-1.2 mg/dL	5.18 ± 8.16	2.24 ± 3.57	9.89 ± 10.81	< 0.001
INR	1.89 ± 1.75	1.43 ± 0.43	2.72 ± 2.55	< 0.001
BUN, 8-12 mg/dL	34.47 ± 35.55	17.63 ± 15.52	61.44 ± 41.49	< 0.001
Creatinine, 0.4-1.2 mg/dL	1.94 ± 1.91	1.27 ± 1.35	3.01 ± 2.17	< 0.001
eGFR, mL/(min·1.73 m^{-2}) (MDRD-4)	63.17 ± 46.12	79.14 ± 37.4	37.57 ± 47.24	< 0.001
eGFR, mL/(min·1.73 m^{-2}) (MDRD-6)	54.87 ± 38.25	70.85 ± 33.29	29.32 ± 31.16	< 0.001
eGFR, mL/(min·1.73 m^{-2}) (CKD-EPI)	65.39 ± 37.49	82.11 ± 30.28	38.59 ± 31.99	< 0.001

Values were expressed as mean ± SD unless otherwise defined. Statistical comparison was performed with Student's t and χ^2 test. MELD: Model for end-stage liver disease; INR: International normalized ratio; BUN: Blood urea nitrogen; eGFR: Estimated glomerular filtration rate; MDRD: Modification of diet in renal disease; MDRD-4: 4-variable MDRD; MDRD-6: 6-variable MDRD; CKD-EPI: The chronic kidney disease epidemiology collaboration; NS: Not significant.

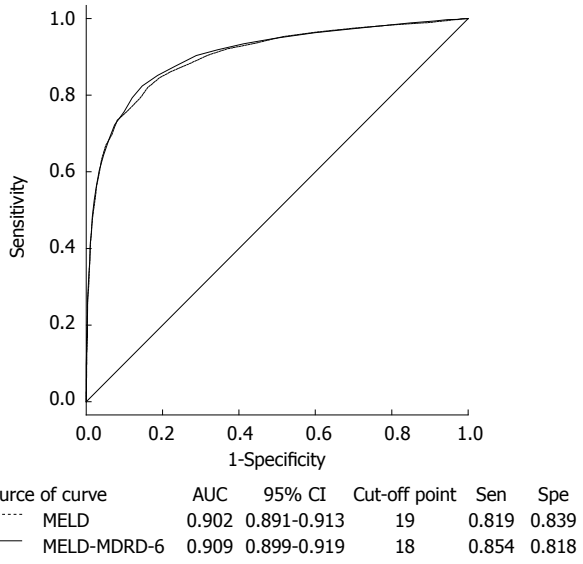

Figure 1 Receiver-operating characteristic curve of the original model for end-stage liver disease and the model for end-stage liver disease-6-variable model for end-stage liver disease score for the prediction of in-hospital mortality. MELD: Model for end-stage liver disease; MDRD: Modification of diet in renal disease; MDRD-6: 6-variable MDRD; AUC: Area under curve; Sen: Sensitivity; Spe: Specificity.

crease in chi-square (2254.88 *vs* 2198.32) and a decrease in -2 log (likelihood) (2703.72 *vs* 2773.90). In the ROC curve (Figure 1), the MELD-MDRD-6 score showed a marginal improvement in area under the curve (0.909 *vs* 0.902), sensitivity (0.854 *vs* 0.819) and specificity (0.818 *vs* 0.839) compared to the original MELD equation. Table 5 compares the MELD and MELD-MDRD-6 equations in patients with different eGFR. The MELD-MDRD-6 equation showed a better predictive value in patients with eGFR ⩾ 90, 60-89, 30-59 and 15-29.

DISCUSSION

This retrospective, cross-sectional study involved a broader population of cirrhotic patients than only data from liver transplant registries. We attempted to incorporate eGFR obtained by different creatinine-based equations into the MELD equation to replace serum creatinine and predict in-hospital mortality. The new equation "MELD-MDRD-6", which incorporates eGFR obtained by the 6-variable MDRD equation, only marginally improves the predictive value compared to the original MELD score.

The MELD score was initially created to predict survival following the elective transjugular intrahepatic portosystemic shunts procedure[4]. This model was subsequently validated as a predictor of survival in several cohort studies for various severities of liver disease. It is also used to determine the prioritization of transplant recipients in the United States[1,4,5]. The existing MELD equation contains 3 variables, each of which was selected on the basis of statistical analysis: INR and total bilirubin, both markers of liver function, and serum creatinine as the third variable, a marker of renal function. This highlights the prognostic value of renal function in cirrhotic patients. In the existing MELD equation, however, the values of bilirubin, INR and creatinine < 1.0 mg/dL are set to 1.0 mg/dL in order to avoid a negative value after

Table 2 Univariate and multivariate logistic regression analyses of the various parameters in predicting in-hospital mortality

Parameter	Beta coefficient	Standard error	Odds ratios (95% CI)	*P* value
Univariate logistic regression analysis				
Age, yr	0.02	0.00	1.02 (1.02-1.03)	< 0.001
Hepatoma	0.95	0.07	2.57 (2.25-2.95)	< 0.001
Ascites	1.47	0.07	4.36 (3.80-5.02)	< 0.001
Hepatic encephalopathy	1.29	0.07	3.62 (3.13-4.19)	< 0.001
Cause of liver cirrhosis (reference group: NBNCNA)				
Hepatitis C	-0.30	0.10	0.74 (0.61-0.91)	0.004
Hepatitis B	-0.17	0.10	0.85 (0.70-1.03)	NS (0.098)
Alcoholic	-0.76	0.11	0.47 (0.38-0.58)	< 0.001
Hepatitis C + hepatitis B	-0.51	0.22	0.60 (0.39-0.92)	0.020
Hepatitis C + alcoholic	-0.53	0.17	0.59 (0.42-0.82)	0.002
Hepatitis B + alcoholic	-0.15	0.36	0.86 (0.42-1.74)	NS (0.670)
Hepatitis C + hepatitis B + alcoholic	-0.47	0.28	0.63 (0.36-1.09)	NS (0.098)
Child–Pugh points	0.67	0.02	1.95 (1.87-2.03)	< 0.001
MELD score	0.22	0.01	1.25 (1.23-1.27)	< 0.001
BUN, mg/dL	0.07	0.00	1.07 (1.06-1.07)	< 0.001
Creatinine, mg/dL	0.72	0.03	2.05 (1.93-2.18)	< 0.001
eGFR, mL/(min·1.73 m^{-2}) (MDRD-4)	-0.04	0.00	0.97 (0.96-0.97)	< 0.001
eGFR, mL/(min·1.73 m^{-2}) (MDRD-6)	-0.05	0.00	0.95 (0.95-0.96)	< 0.001
eGFR, mL/(min·1.73 m^{-2}) (CKD-EPI)	-0.04	0.00	0.97 (0.96-0.96)	< 0.001
Albumin, g/dL	-1.97	0.07	0.14 (0.12-0.16)	< 0.001
Total bilirubin, mg/dL	0.20	0.01	1.22 (1.20-1.25)	< 0.001
INR	1.74	0.08	5.70 (4.87-6.67)	< 0.001
Multivariate logistic regression analysis				
Age, yr	0.03	0.01	1.03 (1.01-1.04)	< 0.001
Hepatoma	0.95	0.13	2.60 (2.02-3.34)	< 0.001
Cause of liver cirrhosis (reference group: NBNCNA)				
Hepatitis C	-0.19	0.18	0.83 (0.58-1.18)	NS (0.299)
Hepatitis B	-0.28	0.19	0.76 (0.52-1.10)	NS (0.139)
Alcoholic	-0.21	0.22	0.81 (0.52-1.25)	NS (0.342)
Hepatitis C + hepatitis B	-1.03	0.40	0.36 (0.16-0.78)	0.010
Hepatitis C + alcoholic	-0.79	0.35	0.46 (0.23-0.90)	0.023
Hepatitis B + alcoholic	0.32	0.57	1.38 (0.45-4.22)	NS (0.576)
Hepatitis C + hepatitis B + alcoholic	0.54	0.47	1.71 (0.68-4.29)	NS (0.354)
MELD score	0.14	0.03	1.14 (1.09-1.20)	< 0.001
BUN, mg/dL	0.04	0.00	1.05 (1.04-1.05)	< 0.001
eGFR, mL/(min·1.73 m^{-2}) (MDRD-4)	0.03	0.01	1.03 (1.02-1.04)	< 0.001
eGFR, mL/(min·1.73 m^{-2}) (MDRD-6)	-0.03	0.01	0.97 (0.95-0.99)	< 0.001
Albumin, g/dL	-1.24	0.13	0.29 (0.22-0.38)	< 0.001
INR	0.24	0.10	1.27 (1.04-1.54)	0.019

MELD: Model for end-stage liver disease; BUN: Blood urea nitrogen; eGFR: Estimated glomerular filtration rate; MDRD: Modification of diet in renal disease; MDRD-4: 4-variable MDRD; MDRD-6: 6-variable MDRD; CKD-EPI: The chronic kidney disease epidemiology collaboration; INR: International normalized ratio; NS: Not significant.

natural logarithmic transformation[16]. Additionally, serum creatinine values > 4.0 mg/dL are capped at 4.0 mg/dL. Setting bilirubin, INR and creatinine levels < 1.0 mg/dL to 1.0 mg/dL implicitly assumes that mortality at 1.0 mg/dL is the same as at levels < 1.0 mg/dL. This assumption is problematic since the increase in serum creatinine from 0.3 mg/dL to 0.6 mg/dL usually reflects a 50% decrease in the eGFR, which could be defined as acute kidney injury. On the other hand, 45.81% of all patients (1767 patients) and 15.52% of all non-survivors (230 patients) had a creatinine value of < 1.0 mg/dL in this study and it is therefore unreasonable to neglect this group.

When incorporating eGFR into the MELD equation to replace serum creatinine, we set bilirubin and INR to 1.0 mg/dL when the value was < 1.0 mg/dL for the purpose of comparison with the original MELD equation. However, there was no adjustment of the eGFR value when using it for reconstructing new formulas. Compared to the original MELD equation, the new MELD equations preserve the "non-negative property" that MELD-MDRD-4 ranged from 1 to 60, MELD-MDRD-6 ranged from 2 to 60, and MELD-CKD-EPI ranged from 1 to 61. Furthermore, the original MELD score classified patients from 6 to 40; we did not preinstall the upper limit when using them to predict in-hospital mortality. Nonetheless, it might be more accurate or easier to preinstall the upper limit in these new MELD equations.

Serum creatinine, a marker of renal function, is a well-recognized predictor of survival in patients with liver disease and outcome after liver transplantation[6,17,18]. It has been suggested that renal function should be routinely monitored in all patients with advanced cirrhosis, especially those with ascites[17]. Although serum creatinine is the most useful and widely accepted indicator for

Table 3 Relationship between estimated glomerular filtration rate, total bilirubin, international normalized ratio and model for end-stage liver disease score as a predictor of in-hospital mortality

Model	Variable	Odds ratio (95% CI)	*P* value	χ^2	-2 Log Likelihood
Model 1	MELD	1.25 (1.23-1.27)	< 0.001	2198.32	2773.90
Model 2	Total bilirubin[1]	2.25 (2.05-2.48)	< 0.001	2161.45	2810.77
	INR[1]	6.14 (4.56-8.27)	< 0.001		
	eGFR (MDRD-4)[1]	0.22 (0.20-0.25)	< 0.001		
Model 3	Total bilirubin[1]	2.17 (1.97-2.40)	< 0.001	2293.82	2664.79
	INR[1]	5.95 (4.39- 8.06)	< 0.001		
	eGFR (MDRD-6)[1]	0.19 (0.17-0.22)	< 0.001		
Model 4	Total bilirubin[1]	2.26 (2.05-2.48)	< 0.001	2199.16	2773.07
	INR[1]	6.28 (4.65-8.49)	< 0.001		
	eGFR (CKD-EPI)[1]	0.20 (0.18-0.23)	< 0.001		

[1]Loge value. Statistical comparison was performed with logistic regression analysis. MELD: Model for end-stage liver disease; INR: International normalized ratio; eGFR: Estimated glomerular filtration rate; MDRD: Modification of diet in renal disease; MDRD-4; 4-variable MDRD; MDRD-6: 6-variable MDRD; CKD-EPI: The chronic kidney disease epidemiology collaboration.

Table 4 Comparison of different models for end-stage liver disease equations for the prediction of in-hospital mortality

Equations	Odds ratio (95% CI)	*P* value	χ^2	-2 Log Likelihood
MELD	1.25 (1.23-1.27)	< 0.001	2198.32	2773.90
MELD-MDRD-4	1.27 (1.26-1.29)	< 0.001	2147.93	2824.30
MELD-MDRD-6	1.29 (1.27-1.31)	< 0.001	2254.88	2703.72
MELD-CKD-EPI	1.28 (1.26-1.30)	< 0.001	2185.01	2787.21

Statistical comparison was performed with logistic regression analysis. MELD: Model for end-stage liver disease; MDRD: Modification of diet in renal disease; MDRD-4: 4-variable MDRD; MDRD-6: 6-variable MDRD; CKD-EPI: The chronic kidney disease epidemiology collaboration.

estimating renal function in cirrhotic patients[19], it is less sensitive because of the associated reduced muscle mass, severe hyperbilirubinemia and diminished hepatic biosynthesis of creatinine, as well as the low-protein diet given to such patients[1,6,17]. In addition, the original MELD equation regards serum creatinine of < 1.0 mg/dL as 1.0 mg/dL, which leaves approximately 15% to 20% of patients whose survival cannot be accurately predicted by this score[6,9]. For that reason, we replaced serum creatinine by eGFR in the MELD equation. Cystatin C, in contrast to serum creatinine, is a more accurate surrogate marker of renal function since its serum concentration is independent of muscle mass or gender and can be reliably determined in patients with hyperbilirubinemia[20-22]. Theoretically, including cystatin C in a modified MELD score should increase the predictive performance. However, a clinical study in 429 cirrhotic patients showed that a cystatin C-based MELD score has an equal predictive performance compared to the creatinine-based model[23]. In the view of the high cost of cystatin C, more than 10-fold higher than enzymatic creatinine measurement, eGFR probably is more suitable than cystatin C to be incorporated into the MELD equation clinically.

To evaluate the predictive value of the new MELD equation in cirrhotic patients with normal renal function, we grouped patients into 5 groups according to their eGFR (Table 5). MELD-MDRD-6 was more accurate than the original MELD when eGFR was > 15 mL/(min·1.73 m^2) but not when it was < 15 mL/(min·1.73 m^2). There might be 3 reasons for this. Firstly, the MDRD equation tends to overestimate the GFR, especially when GFR was < 40 mL/(min·1.73 m^2)[24]. Secondly, patients receiving renal replacement therapy, whose eGFR is usually < 15 mL/(min·1.73 m^2), were not excluded in the present study. Thirdly, we did not preinstall the upper limit of these new equations which may make a difference for the predictive value.

How about incorporating the measured GFR into the MELD equation? Direct measurement of GFR using exogenous markers remains the major method to assess renal function in cirrhotic patients[1]. In these patients, inulin clearance has been considered the "gold standard" for measuring GFR. Although one study has shown that measured GFR is superior to both serum creatinine and eGFR at predicting outcome in cirrhotic patients[10], this technique requires a continuous intravenous infusion, takes more time for urine collections, is costly and potentially invasive. It is therefore impractical for the repeated assessments of renal function[1,7,17].

Theoretically, estimated GFR calculated by the creatinine-based equations should show a similar prognostic value to serum creatinine. However, both the Cockcroft-Gault and MDRD equations tend to overestimate GFR in patients with cirrhosis; a series has shown that only 66% of estimates were within 30% of the measured GFR[12,24-26]. The Cockcroft-Gault equation is thought to be less accurate than the MDRD equation since it incorporates body weight, which is markedly biased in patients with edema and/or ascites[25]. The MDRD-4 (simplified MDRD) equation is most often used to calculate GFR because it is considered to be as accurate as the original MDRD-6 equation[27]. However, its usefulness has not been proved in healthy individuals and its accuracy may be low in specific clinical settings[26,28]. Therefore, the MDRD-6 equation is considered the best, possibly because it incorporates blood urea nitrogen (BUN) and albumin levels, 2 variables which are abnormal in cirrhotic patients[28]. The CKD-EPI equation, a newly developed equation for estimating GFR, has been proposed as more

Table 5 The difference between the model for end-stage liver disease and model for end-stage liver disease-modification of diet in renal disease-6 scores of differentially obtained estimated glomerular filtration rate for the prediction of in-hospital mortality

eGFR	Equations	Odds ratio (95% CI)	*P* value	χ^2	-2 Log Likelihood
⩾ 90	MELD	1.17 (1.13-1.21)	< 0.001	99.45	609.51
	MELD-MDRD-6	1.20 (1.16-1.24)	< 0.001	114.55	588.67
60-89	MELD	1.22 (1.18-1.26)	< 0.001	185.77	636.17
	MELD-MDRD-6	1.27 (1.22 -1.32)	< 0.001	214.60	606.45
30-59	MELD	1.21 (1.17-1.24)	< 0.001	283.21	755.92
	MELD-MDRD-6	1.26 (1.22-1.30)	< 0.001	312.75	725.22
15-29	MELD	1.25 (1.19-1.30)	< 0.001	163.72	369.37
	MELD-MDRD-6	1.31 (1.24-1.39)	< 0.001	182.49	350.59
< 15	MELD	1.36 (1.27-1.45)	< 0.001	190.62	311.89
	MELD-MDRD-6	1.30 (1.23-1.39)	< 0.001	164.66	337.42

Statistical comparison was performed with logistic regression analysis. MELD: Model for end-stage liver disease; eGFR: Estimated glomerular filtration rate; MDRD: Modification of diet in renal disease; MDRD-4: 4-variable MDRD; MDRD-6: 6-variable MDRD.

accurate than the MDRD equation, especially when GFR is high. It shows less bias, improved precision and greater accuracy[14]. However, it also has not been used in patients with cirrhosis. In the present study, despite the fact that MELD-CKD-EPI showed a better prognostic value than MELD-MDRD-4, it was not better than the original MELD equation or MELD-MDRD-6. Our data showed that MELD-MDRD-6 has the better predictive value for in-hospital mortality compared to other equations. We suppose that it may be associated with the insertion of BUN and albumin as variables; in particular, serum albumin is an excellent predictor of mortality.

Findings about incorporated eGFR into the MELD equation to predict in-hospital mortality, however, need to be interpreted with caution. On the one hand, although statistically significant, the value added from MDRD-6 was limited (increase in the ROC from 0.902 to 0.909). This limited value may not add much to a treatment or decision algorithm or in predicting events. On the other hand, we did not further classify in-hospital mortality according to the causes since the predicted value might be different in different outcomes. Furthermore, the results here might not suitable for patients on the liver transplant waiting list or who are followed up long-term.

It was suggested the presence of diabetes increases the 5 year mortality rate up to 2.52-fold in cirrhotic patients[29]. The previous reports have reported that up to 96% of cirrhotic patients may have glucose intolerance and 30% could be clinically diagnosed as diabetes[30-32]. The etiology of cirrhosis is frequently associated with the prevalence of diabetes, such as non-alcoholic fatty liver disease, alcoholic hepatitis, hepatitis C virus infection and hemochromatosis[33]. Hepatitis C infection could down-regulate insulin receptors and enhance insulin resistance. Although hepatitis C related cirrhosis showed significant impact on in-hospital mortality in our series (Table 2), it lost its significance after entering multivariate analysis. Further prospective study is warranted to confirm the impact of hepatitis C related insulin resistance in cirrhotic patients.

The present study has several limitations. Firstly, the construction of new MELD equations was dependent on logistic regression analysis but not on a time-dependent Cox regression model, which is more appropriate for evaluating patients with continuously changing laboratory data. Secondly, the existing creatinine-based eGFR equations were not constructed for cirrhotic patients. Thus, a specific formula for incorporation into the MELD equation needs to be derived for calculating GFR in these patients in order to provide prognostic values with better accuracy. Thirdly, the study was retrospective and cross-sectional in nature and therefore a prospective cohort study is warranted to test and verify our conclusions.

In conclusion, renal function is an important prognostic factor for patients with cirrhosis and therefore the MELD score showed a good correlation with mortality risk in the patients included in the present study. However, the unreliability of serum creatinine in measuring renal function and the problematic assumption of serum creatinine in the MELD score makes it inaccurate when evaluating cirrhotic patients with early renal function impairment. Although incorporated estimated GFR obtained by the 6-variable MDRD equation into the MELD equation showed an improvement in predicting in-hospital mortality statistically, clinical superiority is negligible. Thus, the important issue is how to better assess true GFR when evaluating renal function in cirrhotic patients.

COMMENTS

Background

Serum creatinine is an unreliable marker for renal function in cirrhotic patients; therefore, the creatinine-based end-stage liver disease (MELD) score may be inaccurate for evaluating cirrhotic patients with normal or mild impaired renal function.

Research frontiers

A specific formula derived for calculating glomerular filtration rate (GFR) in cirrhotic patients is warranted.

Innovations and breakthroughs

Incorporated estimated GFR (eGFR) which is obtained from the 6-variable diet in renal disease [modification of diet in renal disease (MDRD)] equation into the MELD formula has an equal predictive performance to the original creatinine-based MELD formula.

Applications

eGFR which is obtained by the 6-variable MDRD equation could replace serum creatinine in the MELD score.

Terminology

MELD score: A scoring system for assessing the severity of chronic liver

disease, useful in determining prognosis and prioritizing for liver transplant; MDRD: The most widely used equation to calculate GFR.

Peer review

This is a unique paper that investigated whether bone marrow derived cells can contribute to liver fibrosis. The results are easy to understand and very persuasive, although number of mice using the analysis was limited.

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BRIEF ARTICLE

Day-of-surgery rejection of donors in living donor liver transplantation

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Abstract

AIM: To study diagnostic laparoscopy as a tool for excluding donors on the day of surgery in living donor liver transplantation (LDLT).

METHODS: This study analyzed prospectively collected data from all potential donors for LDLT. All of the donors were subjected to a three-step donor evaluation protocol at our institution. Step one consisted of a clinical and social evaluation, including a liver profile, hepatitis markers, a renal profile, a complete blood count, and an abdominal ultrasound with Doppler. Step two involved tests to exclude liver diseases and to evaluate the donor's serological status. This step also included a radiological evaluation of the biliary anatomy and liver vascular anatomy using magnetic resonance cholangiopancreatography and a computed tomography (CT) angiogram, respectively. A CT volumetric study was used to calculate the volume of the liver parenchyma. Step three included an ultrasound-guided liver biopsy. Between November 2002 and May 2009, sixty-nine potential living donors were assessed by open exploration prior to harvesting the planned part of the liver. Between the end of May 2009 and October 2010, 30 potential living donors were assessed laparoscopically to determine whether to proceed with the abdominal incision to harvest part of the liver for donation.

RESULTS: Ninety-nine living donor liver transplants were attempted at our center between November 2002 and October 2010. Twelve of these procedures were aborted on the day of surgery (12.1%) due to donor findings, and eighty-seven were completed (87.9%). These 87 liver transplants were divided into the following groups: Group A, which included 65 transplants that were performed between November 2002 and May 2009, and Group B, which included 22 transplants that were performed between the end of May 2009 and October 2010. The demographic data for the two groups of donors were found to match; moreover, no significant difference was observed between the two groups of donors with respect to hospital stay, narcotic and non-narcotic analgesia requirements or the incidence of complications. Regarding the recipients, our study clearly revealed that there was no significant difference in either the incidence of different complications or the incidence of retransplantation between the two groups. Day-of-surgery donor assessment for LDLT procedures at our center has passed through two eras,

open and laparoscopic. In the first era, sixty-nine LDLT procedures were attempted between November 2002 and May 2009. Upon open exploration of the donors on the day of surgery, sixty-five donors were found to have livers with a grossly normal appearance. Four donors out of 69 (5.7%) were rejected on the day of surgery because their livers were grossly fatty and pale. In the laparoscopic era, thirty LDLT procedures were attempted between the end of May 2009 and October 2010. After the laparoscopic assessment on the day of surgery, twenty-two transplantation procedures were completed (73.4%), and eight were aborted (26.6%). Our data showed that the levels of steatosis in the rejected donors were in the acceptable range. Moreover, the results of the liver biopsies of rejected donors were comparable between the group A and group B donors. The laparoscopic assessment of donors presents many advantages relative to the assessment of donors through open exploration; in particular, the laparoscopic assessment causes less pain, requires a shorter hospital stay and leads to far superior cosmetic results.

CONCLUSION: The laparoscopic assessment of donors in LDLT is a safe and acceptable procedure that avoids unnecessary large abdominal incisions and increases the chance of achieving donor safety.

Key words: Live donor; Laparoscopic assessment; Rejected donors; Day of surgery; Fatty liver

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INTRODUCTION

Living donor liver transplantation (LDLT) has become an acceptable option for patients in need of liver transplantation who are not likely to receive a deceased organ in a timely fashion[1]. The accurate pretransplant evaluation of a potential live donor in LDLT is a major prerequisite for preventing postoperative liver failure and achieving donor safety. The appropriate selection of a donor for LDLT is an important aspect of achieving donor safety. In general, the utilization rate of potential donors is 28.8%[2]. The objective of this work is to present our early experience with exclusion from donation on the day of surgery in LDLT using a laparoscopic assessment technique.

MATERIALS AND METHODS

Sixty-nine potential living donors were assessed for 69 recipients (58 adults and 11 children) between November 2002 and May 2009 after passing all of the phases of donor selection in our protocol. These patients were taken to the operating room for potential donation without laparoscopic assessment. Between May 2009 and October 2010, 30 potential living donors were assessed for 30 recipients (27 adults and 3 children); these patients were subjected to laparoscopic assessment of their livers prior to proceeding with the abdominal incision to harvest part of the liver for donation. In this study, we did not consider patients to be excluded if they were eliminated either in the preliminary nurse coordinator consultation or during the 3 phases of donor evaluation. The donor evaluation protocol in our center proceeded as follows: after a preliminary nurse coordinator consultation, donors with no contraindication to donation and with an ABO-compatible blood group were evaluated in three steps.

Step one of this evaluation included a clinical and social evaluation. A liver profile, hepatitis marker assessment, renal profile, complete blood count, and abdominal ultrasound with Doppler were performed in this step. Step two involved tests to exclude liver diseases and to evaluate the donor's serological status. In addition to these examinations, step two also included an imaging evaluation of the biliary anatomy and liver vascular anatomy using magnetic resonance cholangiopancreatography and a computed tomography (CT) angiogram, respectively. A CT volumetric study was used to calculate the volume of the liver parenchyma. We considered a graft-to-recipient body weight ratio that was equal to or greater than 0.8% to be a safe lower limit for adults, with a maximum percentage of resection in the donor liver of 60%-65%. Step three included an ultrasound-guided liver biopsy, which is a mandatory part of the evaluation; this process was performed under ultrasound guidance and consisted of three tan-core biopsies. Results of 10% or less fat infiltration were accepted if less than 50% of the donor liver was planned for resection.

Step four was first introduced during May 2009 and consisted of a laparoscopic assessment on the day of donation under general endotracheal anesthesia that occurred prior to opening the abdomen. Laparoscopic access to the abdominal cavity for the placement of a 5 mm port was attained using a Veress needle in the sub-umbilical region. A 30 degree laparoscope was used, and the liver was explored for any gross pathologies. We examined at the gross appearance, color, surface and edges of the liver.

Statistical analysis

Statistical analysis were performed with the SPSS software package for Windows (Statistical Product and Service Solutions, version 17.0, SSPS Inc, Chicago, IL, United States). Relevant arithmetic means, standard deviations,

Table 1 The demographic data for donors of the two groups

	Group A donors (n = 65)			Group B donors (n = 22)			P value
	Range	Mean	SD	Range	Mean	SD	
Age, yr	18-42	23.3	6.3	18-40	27.1	5.5	0.6
Weight, kg	46-86	64.7	10.1	51-93	66.8	11	0.38
Height, cm	140-190	166.5	8.4	152-186	169.3	10	0.44
BMI, kg/m^2	14-28.9	23.5	3.4	17.4-28.4	23.3	3.4	0.88

BMI: Body mass index.

Table 2 The hospital stay and analgesia requirements for donors in each group

	Group A donors n = 65			Group B donors n = 22			P value
	Range	Mean	SD	Range	Mean	SD	
Hospital stay, d	4-7	4.9	1.1	4-6	4.8	0.6	0.75
No. of narcotic analgesia doses per admission, doses	3-10	6.3	2.1	2-8	5	1.5	0.42
No. of non-narcotic analgesia doses per admission, doses	10-17	12.9	1.8	12-16	13.1	1.2	0.31

Table 3 Donor complications in the two groups n (%)

	Group A donors n = 65	Group B donors n = 22	P value
Minor biliary leak	3 (4.6)	1 (4.5)	0.78
Wound seroma/hematoma	4 (6.2)	1 (4.5)	0.98
Wound infection	1 (1.5)	0	0.56
Incisional hernia	1 (1.5)	0	0.56
Ascites	1 (1.5)	0	0.56

numbers and percentages were measured. Categorical parameters were compared using the chi-square test, whereas numerical data were compared using the t test. A P value < 0.05 was considered to be statistically significant.

RESULTS

Ninety-nine LDLT operations were attempted at our center between November 2002 and October 2010. Twelve of these procedures were aborted on the day of surgery (12.1%) due to donor findings, and 87 transplants were completed (87.9%).

These 87 liver transplants were divided into the following groups: Group A, which included 65 transplants that were performed between November 2002 and May 2009, and Group B, which included 22 transplants that were performed between the end of May 2009 and October 2010.

The group A donors consisted of 51 males and 14 females (78.5% and 21.5% respectively), and the group B donors consisted of 15 males and 7 females (68.2% and 31.8 respectively) with a P value of 0.49 for the gender distribution. The donors were also found to be matched between groups with respect to other demographic data, as indicated in Table 1.

Table 4 The indications for liver transplantation in each group of recipients n (%)

	Group A recipients n = 65	Group B recipients n = 22	P value
HCV cirrhosis	29 (44.6)	10 (45.4)	0.95
HBV cirrhosis	11 (16.9)	3 (13.6)	0.98
HBV and HCV cirrhosis	1 (1.5)	2 (9)	0.32
HCC	14 (21.5)	8 (36.3)	0.27
Cryptogenic cirrhosis	8 (12.3)	2 (9)	0.98
Wilson's disease	3 (4.6)	0	0.73
Hyperoxaluria	4 (6.2)	0	0.55
Biliary atresia	0	2 (9)	0.1

HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus.

Table 5 Incidence of complications and retransplantation in each group of recipients n (%)

	Group A recipients n = 65	Group B recipients n = 22	P value
Biliary complications	20 (30.7)	9 (40.9)	0.50
Hepatic artery thrombosis	3 (4.6)	1 (4.5)	0.98
Portal vein thrombosis	4 (6.2)	1 (4.5)	0.78
Incisional hernia	3 (4.6)	2 (9)	0.80
Small-for-size syndrome	3 (4.6)	1 (4.5)	0.98
Primary non-function	1 (1.5)	0	0.56
Retransplantation	7 (10.8)	0	0.29

No significant difference was observed between the donor groups regarding either hospital stay or requirements for narcotic or non-narcotic analgesia, as presented in Table 2. Similarly, as presented in Table 3, no significant difference was observed in the incidence of complications between donor groups.

In group A, the recipients were 46 males and 19 females (70.8% and 29.2% of the recipients, respectively), whereas in group B, the recipients were 15 males and 7 females (68.2% and 31.8% of the recipients, respectively), with a P value of 0.82 for the gender distribution.

The group A recipients ranged in age between 1 and 63 years, with a mean of 40.8 ± 19.4 years. The ages of the recipients in group B ranged between 1 and 68 years, with a mean of 47.6 ± 22.2 years. There was a P value of 0.3 between groups. Table 4 provides the indications for liver transplantation in each group.

The recipients in group A had hospital stays ranging from 10-104 d with a mean of 30.1 ± 17 d. By contrast, the recipients in group B had hospital stays of between 12 and 98 d, with a mean of 31.2 ± 21.7 d (P = 0.75). Table 5 addresses the morbidity of both groups by reporting the incidence of different complications, including retransplantation. This table clearly indicates that there were no significant differences between the groups with respect to the incidence of different complications or retransplantation.

Within the first 2 years after liver transplant, 15 recipients died in group A compared with four deaths among group B recipients (23.1% and 18.2%, respectively, of

Table 6 Causes of graft-related deaths in both groups

	Group A recipients *n* = 65	Group B recipients *n* = 22	*P* value
Total number of graft-related deaths	13	3	0.73
Cholestatic HCV recurrence	1	0	0.56
HCC recurrence	2	0	0.99
Sepsis	3	1	0.99
Hepatic artery thrombosis	2	0	0.99
Portal vein thrombosis	3	2	0.80
Small-for-size syndrome	1	0	0.56

HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma.

Table 7 The incidence of abnormal liver biopsy findings in groups A and B *n* (%)

	Group A donors *n* = 65	Group B donors *n* = 22	*P* value
Steatosis < 5%	18 (27.7)	5 (22.7)	0.86
Steatosis 5%-10%	4 (6.2)	2 (9)	0.64
Steatosis 10%-15%	6 (9.2)	0	0.32
Steatosis 15%-20%	1 (3.1)	0	0.56
Fibrosis (stage 0-1)	1 (1.5)	0	0.56

the recipients in each group; $P = 0.85$).

Two of the deaths in group A were non-graft-related (one patient died from a pulmonary embolism, and the other died from massive bleeding caused by colonic angiodysplasia), whereas only one patient died due to non-graft-related causes in group B (cerebrovascular stroke). Table 6 lists the different causes of graft-related mortalities in the liver transplant recipients in both groups. This table clearly demonstrates that there were no significant differences between the groups with respect to either the total number of graft-related deaths or the individual causes of these graft-related deaths.

Day-of-surgery donor assessment procedures at our center have been conducted by two methods, open and laparoscopic, over two different periods of time (eras). In the first era, 69 LDLT procedures were attempted between November 2002 and May 2009. Upon the open exploration of the donors on the day of surgery, 65 donors were found to have livers with a grossly normal appearance, and 4 donors (2 males and 2 females) were found to have pale, fatty livers. One donor was found to have a pale and grossly steatotic liver, and we decided to biopsy this liver. The biopsy of this liver revealed hepatic steatosis of less than 10%, and we therefore opted to complete the procedure; unfortunately, however, the recipient of this graft developed primary non-function. In the laparoscopic era, 30 procedures were attempted between the end of May 2009 and October 2010. Twenty-two procedures were completed (73.4%), and 8 were rejected (26.6%) on the day of surgery after laparoscopic assessment. Four of the rejected donors were males, and

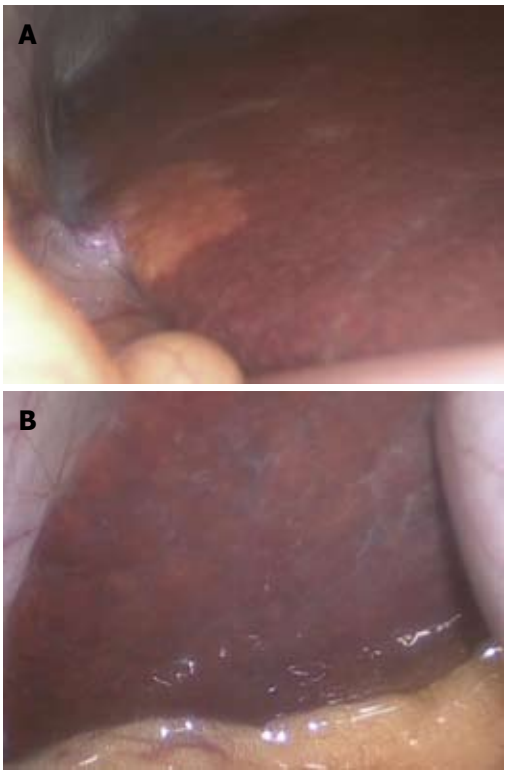

Figure 1 Diagnostic laparoscopy of potential live liver donor. A: Showing pale, fatty liver with localized fat adjacent to the falciform ligament; B: Showing grossly fibrotic appearance.

four were females. The rejected livers were found to be pale and grossly fatty (Figure 1) with rounded borders in seven cases (87.5%) and to have a grossly fibrotic appearance in the remaining case (12.5%).

The body mass index for the rejected donors ranged from 20 kg/m^2 to 28.4 kg/m^2 with a mean of 23.8 ± 1.2 kg/m^2. All of the rejected donors had preoperative liver biopsies, and only four of the patients demonstrated any abnormalities. Three of the rejected donors (25%) exhibited less than 5% steatosis, and one patient (8.3%) demonstrated between 5% and 10% steatosis. These data revealed that the rejected donors had steatosis in the acceptable range. Moreover, the results of the liver biopsies of rejected donors were comparable between group A and group B donors. Table 7 reports the incidence of abnormal liver biopsy findings in the donors of both groups.

DISCUSSION

Donor safety is the most crucial aspect of LDLT programs. The aim of donor evaluation protocols is to completely avoid donor mortality and minimize both the incidence and degree of donor morbidity. Living liver donation is associated with a small but real possibility of mortality that may approach 0.5%[3,4]. Ringe *et al*[5] reported 33 donor deaths and categorized them according to different degrees of certainty. Clavien *et al*[6] defined five grades of postoperative complications for the specific

procedure of LDLT[7]. Morbidity rates vary from 8% to 35% after right-lobe liver donation[8-13] and from 9% to 40% following left or left lateral segment donation[14].

Liver biopsy is a routine step in donor evaluation in a high percentage of LDLT programs. Other methods to evaluate the fat content of the donor's liver are less sensitive and specific than liver biopsy, and these alternatives are unable to detect any associated liver pathology. Unfortunately, liver biopsy is an invasive technique and is associated with a certain risk of complications. Recent studies have reported an incidence of major complications related to liver biopsy of 1.3%[15-17].

The risk of primary non-function after the transplantation of a steatotic graft increases in proportion with the degree of steatosis. Steatosis reduces the functional hepatic mass for both the donor and the recipient, reduces the hepatic regenerative capacity and increases the risk of injury caused by cold ischemia by altering the cell membrane fluidity or disrupting the microcirculation[18-20]. In our LDLT program, we accept up to 10% steatosis for liver grafts.

In our institution, the rate of finding a grossly fatty liver despite an acceptable liver biopsy result was approximately 5.7%. In one of the completed LDLT procedures, the liver was grossly fatty and pale; despite repeated liver biopsies that revealed an acceptable percentage of steatosis, the recipient's post-transplantation course was complicated by primary graft non-function. This incident could indicate that relative to liver biopsy, gross liver morphology may be a more sensitive method of detecting fatty livers. Further randomized studies should be conducted to clarify this point.

According to our small series of laparoscopic donor assessments, this method proved to be both safe and useful in detecting fatty livers by gross morphology. Laparoscopic assessment provides many advantages over the assessment of donors by open exploration; in particular, it causes less pain, requires a shorter hospital stay, and achieves far superior cosmetic results.

The approximately 4- to 5-fold increase in the detection of gross liver steatosis using this method could be related to differences in samples and could indicate more sensitivity but not necessarily more specificity in detecting steatotic livers. However, this statement must be confirmed in a prospective study. Donor safety is a critical concern in LDLT, and laparoscopic donor assessment proved to be a safe and useful adjunctive measure to liver biopsy in the detection of steatotic livers. Further study is required to confirm these results.

COMMENTS

Background

Donor safety is considered to be the most important concern for transplant centers, health authorities and the general community. This consideration is attributed to the ethical concerns that relate to the process of donation from a perfectly healthy person who could suffer an adverse effect on his health following donation. Because the first mission of medicine is to do no harm, the issue of donor safety is extremely critical. Detailed and accurate pretransplant evaluation of a potential donor of a portion of the liver for the sake of living donor liver transplantation (LDLT) is of paramount importance in ensuring donor safety and graft quality, which will translate into better outcomes for both the donor and the recipient.

Research frontiers

Unfortunately, donor pretransplant evaluation, including liver biopsy, cannot absolutely ensure the adequacy of a potential donor, and further evaluation is needed through inspection of the liver. This inspection can only be achieved by exploration of the donor's liver, which requires a large abdominal incision and its inherent sequelae of cosmoses, healing, analgesia requirements, hospital stay and return to work. The accomplishment of this exploration without the requirement of a large incision would represent an improvement for donors.

Innovations and breakthroughs

The introduction of laparoscopy allowed for primary abdominal exploration without the need for a large incision. This exploration enables an excellent assessment of the donor's liver, particularly for steatosis, which can be patchy and therefore easily missed by liver biopsy.

Applications

The study results suggest that the laparoscopic assessment of donors for LDLT is a safe and acceptable procedure. The procedure avoids an unnecessarily large abdominal incision, allows for the more accurate assessment of the liver and increases the chance of achieving donor safety.

Terminology

Liver transplantation refers to the replacement of a diseased liver with either an entire healthy liver or a portion of a healthy liver. Living donor liver transplant is the transplant of part of the liver from a healthy person (the donor) into the recipient. Laparoscopy is the visualization of the abdominal cavity through a very small incision using a specialized camera that transmits the images to a display system (monitor).

Peer review

In this manuscript, the authors describe the utility of laparoscopic assessment of donor livers on the day of transplantation surgery. Because steatosis may be patchy and may be missed on a small core biopsy sample, the results show that the gross examination of the liver by laparoscopic assessment may result in the rejection of unacceptable donors on the day of surgery without subjecting the donors to an open procedure.

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BRIEF ARTICLE

Surgical resection plus biotherapy/chemotherapy improves survival of hepatic metastatic melanoma

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Abstract

AIM: To analyze the correlation of treatment method with the outcome of all the hepatic metastatic melanoma (HMM) patients from our hospital.

METHODS: There were altogether nine cases of HMM that had been treated in the PUMCH hospital during the past 25 years, from December 1984 to February 2010. All of the cases developed hepatic metastasis from primary cutaneous melanoma. A retrospective review was performed on all the cases in order to draw informative conclusion on diagnosis and treatment in correlation with the prognosis. Clinical features including symptoms, signs, blood test results, B-ultrasound and computed tomography (CT) imaging characteristics, and pathological data were analyzed in each case individually. A simple comparison was made on case by case basis instead of performing statistical analysis since the case numbers are low and patients were much diversified in each item that has been analyzed. Literatures on this subject were reviewed in order to draw a safe conclusion and found to be supportive to our finding in a much broad scope.

RESULTS: There are six males and three females whose ages ranged 39-74 years old with an average of 58.8. Patients were either with or without symptoms at the time of diagnosis. The liver function and tumor marker exam were normal in all but one patient. The incidence of HMM does not affect liver function and was not related to virus infection status in the liver. Most of these HMM patients were also accompanied by the metastases of other locations, including lung, abdominal cavity, and cervical lymph nodes. Ultrasound examinations showed lesions ranging 2-12 cm in diameter, with no- or low-echo peripheral areola. Doppler showed blood flow appeared inside some tumors as well as in the surrounding area. CT image demonstrated low density without uniformed lesions, characterized with calcification in periphery, and enhanced in the arterial phase. Contrast phase showed heterogeneous enhancement, with a density higher than normal liver tissue, which was especially apparent at the edge. Patients were treated differently with following procedures: patients #1, #6 and #8 were operated with hepatectomy with or without removal of primary lesion, and followed by comprehensive biotherapy/chemotherapy; patient #9 received hepatectomy only; patient #2 received bacille calmette-guerin treatment only; patient #7 had Mile's surgery but no hepatectomy; and patients #3, #4 and #5 had supportive treatment without specific measurement. The patients who had resections of metastatic lesions fol-

lowed by post-operative comprehensive therapy have an average survival time of 30.7 mo, which is much longer than those did not receive surgery treatment (4.6 mo). Even for the patient receiving a resection of HMM only, the post-operative survival time was 18 mo at the time we reviewed the data. This patient and the patient #6 are still alive currently and subjected to continue following up.

CONCLUSION: Surgical operation should be first choice for HMM treatment, and together with biotherapy/chemotherapy, hepatectomy is likely to bring better prognosis.

Key words: Malignant melanoma; Hepatic metastatic tumor; Hepatectomy; Hepatic metastatic melanoma; Prognosis; Biotherapy; Chemotherapy

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INTRODUCTION

Melanoma is one of the diseases with the highest mortality even though it has a low incidence rate in Chinese population. According to World Health Organization report in 2001, there are only 0.22 and 0.17 incidents per 100 000 among male and female population in China respectively[1]. Depending on the difference in the characteristics of primary tumor, up to one third of melanoma patients will eventually develop metastasis[2,3]. Nearly 40% of the ocular melanoma patients develop hepatic metastasis upon initial diagnosis, and majority of the patients with metastatic melanoma will involve liver[4,5]. The cutaneous melanoma metastasizes to liver less frequently and usually involves other organs as well; however, still 15%-20% of the disseminated diseases occur in liver[6,7]. The median survival time for melanoma patients who developed hepatic metastasis is reported to be less than 5 mo, with a one-year survival rate being 10%[8-10]. Patients with primary cutaneous melanoma may develop more systematic metastasis and resection of hepatic metastatic lesions alone may not be enough to extend patients' survival time[11]. Some studies[12,13] suggested more systematic approaches including chemotherapy and immunotherapy in combination with surgery as treatment of choice.

In this study, we reviewed 9 cases of hepatic metastatic melanoma (HMM) who had been treated in our hospital in the past 25 years, all of whom developed hepatic metastasis from primary cutaneous melanoma. We took a close look at the diagnosis and treatment in comparison with the prognosis, from which we intended to summarize out useful information for future work.

MATERIALS AND METHODS

Based on the clinical documentation of 9 patients of HMM in our hospital from December 1984 to February 2010, we analyzed each case on their clinical symptoms, signs, and blood test results, B-ultrasound and computed tomography (CT) imaging characteristics, pathological data, and treatment and prognosis. A simple comparison was made on case by case basis instead of performing statistical analysis since the case numbers are low and patients were much diversified in each item that has been analyzed. Literatures on this subject were reviewed in order to draw a safe conclusion and found to be supportive to our finding in a much broad scope.

RESULTS

Of these nine patients, there are six males and three females whose ages ranged 39-74 years old with an average of 58.8. As shown in Table 1, all patients had histories of primary cutaneous melanoma at various origins. The time intervals between the diagnosis of the primary melanoma and the discovery of hepatic metastatic lesion also varied, ranging from immediate after original diagnosis to 16 years. Most of these HMM patients was also accompanied by the metastases of other locations, including lung, abdominal cavity, and cervical lymph nodes (Table 1).

Clinical symptoms

Clinical symptoms varied among the nine patients. Three were asymptomatic at initial clinic visit; hepatic lesions were discovered only when they received routine examinations or post-operative follow-up. Two had hematochezia; two presented with fever, abdominal pain accompanied by nausea, vomiting, and diarrhea; one had nausea, vomiting, and diarrhea only and one had hemorrhinia.

Laboratory exams

The incidence of HMM is not related to liver function or virus infection status in the liver. Among the nine cases, only one patient was hepatitis B surface antigen positive with elevated alanine transaminase and aspartate aminotransferase levels. One was hepatitis B core antibody (HBcAb) positive. All others have negative blood exams for hepatitis B or C. Liver functions of all the

Table 1 General information of the patients with hepatic metastatic melanoma

Case	Age (yr)	Gender	Primary melanoma lesion	Interval time before hepatic metastasis (yr)	Accompanying metastasis	Treatments	Survival time (mo)
1	39	M	Sclerotica	7	Spleen	Hepatectomy + comprehensive treatment	30
2	49	M	Left choroid	16	None	Puncture and biopsy + BCG	4
3	51	F	Rectum	0	Abdominal cavity	Biopsy + supportive therapy	1.5
4	69	M	Right lower eyelid	11	Recurrence of carcinoma *in situ*; metastasis to right hip	Biopsy + supportive therapy	2
5	68	M	Nasal cavity	0.6	Bilateral lung, pleura and cervical lymph nodes	Biopsy + supportive therapy	1.5
6	61	F	Back	8	None	Hepatectomy + comprehensive treatment	29
7	70	F	Resctum	1.5	Recurrence of carcinoma *in situ*	Mile's surgery	14
8	48	M	Right 5th dactylus	0.5	Recurrence of carcinoma *in situ*	Hepatectomy, resection of primary lesion + comprehensive treatment	33
9	74	M	Sole	9	Inguinal lymph nodes	Hepatectomy	18

Table 2 The characteristics on imaging of the hepatic metastatic melanoma

Case	Tumor location	Tumor size	B-ultrasound	Computed tomography
1	Right liver	4.3 cm × 3.3 cm × 3.1 cm	NA	NA
2	Multiple	5 mm-12 cm	Low echo	Low density
3	Multiple		NA	Low density
4	Left liver	2.4 cm × 2.5 cm	Low echo, with partially peripheral dense echo	NA
5	Right liver	6.4 cm × 5.0 cm	Low echo, with peripheral low-echo areola, and a bit of strip blood flow inside	Low density
6	Multiple	5 mm-3 cm	Low echo, with peripheral low echo areola	Low density, with higher density peripherally
7	Left liver	2.5 cm × 2.1 cm	Mid-dense echo	Low density, with nodular enhancement
8	Multiple	5 mm-2.6 cm	Low echo	NA
9	Right liver	10 cm × 8 cm	No echo, with septum, and hyperechoic lesion	Cystic mass, with mild enhancement

NA: Not available.

patients were ranked Child-Pugh grade A. Five patients had their alpha fetoprotein (AFP) tested; the patient with HBcAb positive had a level of 348.9 ng/mL while the others were all in the normal range. Five patients had their blood tested for carcinoembryonic antigen (CEA) and cancer antigen (CA)19-9, all of whom had normal levels with CEA < 3.5 ng/mL and CA19-9 < 35 U/mL. Initial routine blood tests on two patients with fever showed increased white blood cells while the other seven were normal. Lower hemoglobin was found in patients with hematochezia or hemorrhinia or symptom of nausea, vomiting, and diarrhea.

Imaging exam

Ultrasound examinations showed lesions ranging 2-12 cm in diameter, with no- or low-echo peripheral areola. Doppler showed blood flow appeared inside some tumors as well as in the surrounding area. Six patients had CT scans, the non-contrast phase showed low density solid masses, with two cases close to the water density. The lesions had heterogeneous density inside and peripheral calcification (Table 2). Contrast phase showed heterogeneous enhancement, with a density higher than normal liver tissue, which was especially apparent at the edge (Figure 1).

All cases had histology confirmation of malignant melanoma for both primary and metastatic lesions.

Treatment

One patient (#1) had a surgical resection of the hepatic metastatic lesion, followed by six courses of chemotherapy with unclear dose using dacarbazine (DTIC)/interleukin 2 (IL-2)/interferon (IFN)/cisplatin (DDP) when further hepatic metastasis arose. One (#6) had a resection of hepatic metastatic lesion and six courses of chemotherapy using DDP/IL-2/IFN every other day. One (#8) received the primary lesion surgery and four courses of biotherapy/chemotherapy using DTIC/IL-2/IFN. All these patients had a survival time more than 29 mo. Another patient (#9) had no recurrence yet for 18 mo after hepatectomy only. This patient is the one we are continuing to follow up currently. One (#7) had a resection of the primary melanoma and celiac metastatic solid mass. One patient (#2) had liver lesion biopsy, received six courses of BCG 75 g. Three patients (#3, 4 and 5) only received supportive treatment. The average survival time of the last five patients is only 4.6 mo after diagnosis. The patients who had resections of primary and metastatic lesions followed by post-operative comprehensive therapy tended to have longer survival times (Table 1).

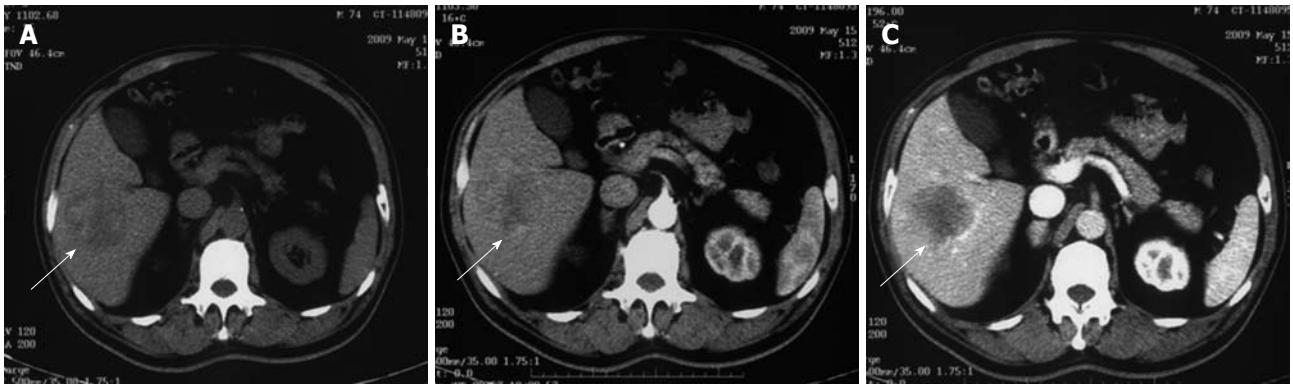

Figure 1 The hepatic metastatic melanoma was shown by computed tomography image on different phases. A: Non-contrast; B: Arterial phase; C: Portal vein phase. The lesion (arrow) showed low density without uniform, enhanced in the arterial and portal phase.

DISCUSSION

HMM is a rare disease in China. As one of the best hospitals in China, we only collected 9 cases in a span of 25 years. The symptoms of the patients were often observed in the main clinical manifestations of HMM including both the symptoms of the primary lesions and those of the hepatic metastasis. Early-stage patients can be asymptomatic; enlarged tumors can cause distention, discomfort, gastrointestinal symptoms, *etc*[14]. Since most patients have explicit histories of primary lesion, HMM should be considered as hepatic lesion being detected.

Under B-ultrasound, HMM is mainly manifested as low echo or even no echo, and frequently heterogeneous. Sometimes a solid neoplasm bulging to the cystic mass can be seen. Doppler shows peripheral surrounding blood flow, presenting as a bull's-eye configuration[15], which suggests a likely hepatic metastatic tumor.

In CT scan, HMM is shown as a solid mass of heterogeneous density: low density and even cystic degeneration in the center, and circular irregular higher density and even calcification in the periphery, presenting as the "rosette sign"[16] (Figure 1A). Enhanced CT scans show that HMM is rich in blood supply, as the arterial phase (Figure 1B) is apparently enhanced while the portal vein (Figure 1C) and delay phases have decreased density. It is similar to the signs of hepatocellular carcinoma, but mainly manifests as circular enhancement in general[17].

Similar to the former studies, this study also showed that routinely tested tumor markers, such as AFP and CA series, are not helpful in the clinical diagnosis of HMM[14]. New biomarkers have been evaluated but not yet in clinical application[18]. As HMM can be of various tissue origin, different cell morphologies, arrangement structures, or amounts of melanin pigment are observed. The final diagnosis of malignant melanoma mainly relies on pathological examination and immunohistochemistry staining.

Therapeutic options for HMM were few with limited effectiveness. It includes surgical resection, systemic or local catheterized chemotherapy, radiotherapy, immunotherapy, and biotherapy. Response rate to chemotherapy is only 10%-30%, and it differs significantly between ocular and cutaneous melanoma[19,20]. For patients with primary ocular melanoma, the response rate to chemotherapy is extremely low. However, percutaneous hepatic perfusion, as a novel approach to chemotherapy delivery, has been applied in clinic[21]. With ocular melanoma, a 50% overall response rate was observed, including two complete responses[22]. Also other methods such as hepatic artery chemoembolization resulted in radiologic response (38.9%) or disease stabilization (47.2%) in most patients[23]. Nevertheless, the median overall survival and time to progression of liver disease were 7.7 mo and 6 mo, respectively.

Some researchers have proposed that chemotherapy combined with biotherapy using IL-2, IFN, *etc*., could increase the response rate and prolong survival time[13]. When data were pooled, biochemotherapy was superior to chemotherapy in response and delayed progression at 6 mo, but not in decreased mortality at 12 mo. However, this regimen may need further exploration because of the toxicity of biochemotherapy, which may induce serious complications and significantly affect patient's quality of life[24].

Surgical resection has been shown to prolong the survival time, since metastatic lesions for primary ocular melanoma are usually confined in liver[5]. Although the recurrence rate is high, ocular melanoma patients tend to remain disease free longer than cutaneous patients[11]. Recently, investigators have indicated that for patients without metastasis to extrahepatic organs, resection of hepatic metastatic lesions may prolong the survival times, with apparently a higher 2-year survival rate than that of chemotherapy, biotherapy, or supportive therapy alone[25-28]. Meyer *et al*[29] also imply surgical resection could apparently prolong the survival time even if the metastatic lesion is resected palliatively. Aoyama *et al*[30] has reported at an earlier time that after resection, recurrence-free and overall 5-year survival rates of those patients were 15.6% and 53.3%, respectively. Other reports also demonstrated advantages of resection over non-surgical measurement[31,32]. It has reported that combination therapy of resection with TIL treatment dramatically improved survival[33]. In our case, three patients received resection plus comprehensive therapy, and all had survival times longer than 2 years. Even for the patient receiving a resection of primary lesion only, the post-operative

survival time was longer than 1.5 year. Two patients with hepatectomy (#6, 9) are still living currently under following up. These results suggested that resection of the primary and HMM lesions and/or in combination with chemotherapy and immunotherapy may enhance the effectiveness of the treatment and prolong survival time, even with other extrahepatic lesions. Further study with larger number of the patients is needed to accumulating the evidence.

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COMMENTS

Background

Melanoma is a disease with the highest mortality but low incidence rate in Chinese population. Liver metastasizes is very common in melanoma. The median survival time for melanoma patients who developed hepatic metastasis is reported to be less than 5 mo, with a one-year survival rate being 10%. Therapeutic options for hepatic metastatic melanoma (HMM) were few with limited effectiveness. Surgical resection has been shown to prolong the survival time. This study provides useful information on making right decision on treatment method on HMM patient for better prognosis.

Research frontiers

The hotspots or important area for HMM is how to choose the best treatment method in order to obtain maximum survival time.

Innovations and breakthroughs

The finding provides further evidence on the conclusion that resection of the primary and HMM lesions and in combination with chemotherapy and immunotherapy may enhance the effectiveness of the treatment and prolong survival time.

Applications

This paper, together with other related publications, can be collectively instructive to oncologists in their practice in treat HMM patients.

Terminology

HMM: Hepatic metastatic melanoma, is a metastatic tumor originated from melanoma.

Peer review

In this study, authors describe their experience on 9 patients with HMM and surgical resection in some of them. They concluded that surgical operation in this pts should be firstly considered, which in association with biochemotherapy, has better prognosis. The manuscript is well prepared.

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CASE REPORT

Acute liver failure complicating jejunojejunal intussusception presentation in a gastric bypass patient

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Abstract

Over 200 000 weight loss procedures are performed annually in the United States. Physicians must therefore be cognizant of the unique array of complications associated with these procedures. We describe a case of jejunojejunal intussusception in a gastric bypass patient who presented with acute liver failure (ALF) due to acetaminophen (APAP) toxicity. Our patient is a 29 year-old female who had undergone Roux-en-Y gastric bypass surgery seven years prior. She was evaluated in the emergency department for confusion. Her family reported a 3-wk history of progressive abdominal pain and vomiting, for which she had ingested 40 acetaminophen/oxycodone tablets over the past 2 d. Physical examination showed icteric sclerae, a distended abdomen, and grade I encephalopathy. She fulfilled the criteria for ALF and was listed for liver transplantation. Abdominal computed tomography scan revealed a jejunojejunal intussusception. She underwent emergent exploratory laparotomy and resection of the infarcted intussusceptum and the previous jejunojejunostomy. She had rapid clinical improvement, with decreasing liver enzymes and improved hepatic synthetic function. She had complete resolution of coagulopathy and encephalopathy, and was removed from the liver transplant list. She was discharged home 20 d after hospitalization with normal liver tests. This case demonstrates that acute abdominal catastrophes can potentiate liver injury in the setting of acetaminophen toxicity. Encephalopathy may obscure history and physical exam findings. This case also exemplifies the pitfalls in the management of the bariatric surgery patient and the importance of multispecialty collaboration in patients presenting with organ failure.

Key words: Acute liver failure; Gastric bypass; Intussusception; Acetaminophen toxicity

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INTRODUCTION

Acute liver failure (ALF) is an uncommon but catastrophic illness, with an estimated annual incidence of

2000 cases in the United States[1]. It is defined as coagulopathy (international normalized ratio ⩾ 1.5) and encephalopathy without pre-existing liver disease, of less than 26 wk duration[1]. Drugs and toxins account for the majority of cases of ALF, followed by acute viral hepatitis A and B. Of ALF cases, 15%-20% have no identifiable cause despite extensive clinical investigation[1].

The mortality rate of acute liver failure approaches 85%. However, approximately 15%-20% of patients with fulminant or subfulminant hepatic failure will improve spontaneously[2]. Of the treatments available for the management of ALF, emergency orthotopic liver transplantation is one of the best interventions with 3-year survival rates of 50%-75%[2,3].

CASE REPORT

A 29-year-old female with altered mental status was brought to the Emergency Department by her family. She had undergone a Roux-en-Y gastric bypass procedure seven years prior. According to her family, she had progressive abdominal pain and vomiting for three weeks. She had ingested 40 tablets of acetaminophen/oxycodone (acetaminophen total dose 13 000 mg) to control her abdominal pain over the previous two days, prescribed by her family physician while awaiting further outpatient evaluation. Her physical examination showed icteric sclerae, a distended abdomen, and grade I encephalopathy. Her laboratory values are summarized in Table 1. Her model for end Stage liver disease score was 41. She fulfilled the criteria for ALF and was promptly listed for liver transplantation. Her creatinine at admission was elevated to 4.7 and she was oliguric. She was started on N-acetylcysteine and was admitted to the intensive care unit.

Hepatic ultrasound revealed a mildly enlarged liver measuring 21.4 cm that was otherwise normal in echotexture and contour. Due to her history of abdominal pain, a computed tomography scan of her abdomen was also obtained, which revealed a jejunojejunal intussusception (Figure 1).

Based on these findings, the patient underwent an emergent exploratory laparotomy and resection of the intussuscepted bowel and the entire jejunojejunostomy. The jejunojejunostomy was patulous, with 45 cm portion of her common channel intussuscepted in an antiperistaltic fashion into her jejunojejunostomy (Figure 2). The intussusception was unable to be reduced and succus was found leaking from this site, which suggested bowel necrosis. The jejunojejunostomy was opened and the intussusceptum was found to be infarcted (Figure 3). The necrotic bowel was resected *en bloc*, and the patient was left in gastrointestinal discontinuity. A planned second look operation was conducted to assess the viability of the Roux limb, which was at risk for ischemia as its vascular pedicle was violated on resection of the jejunojejunostomy. Two days after her first surgery, her gastrointestinal continuity was restored. At the same procedure, a liver biopsy was performed which showed extensive pericentral hepatocyte dropout and central-

Table 1 Significant laboratory results upon patient's initial presentation

Laboratory results	
Aspartate aminotransferase	5681 U/L
Alanine aminotransferase	6705 U/L
Total bilirubin	3.1 mg/dL
Direct bilirubin	2.5 mg/dL
International normalized ratio	4.5
Creatinine	4.7
Acetaminophen level	138
Hepatitis B	Negative
Hepatitis C	Negative
Urine drug screen	
Benzodiazepine	Positive
Phencyclidine	Positive
Opiates	Positive

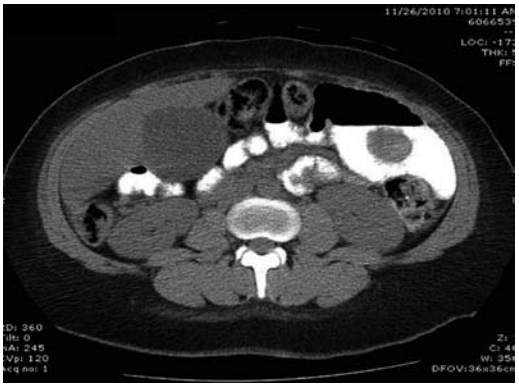

Figure 1 Jejunojejunal intussusceptions seen in left hemiabdomen.

central bridging necrosis, consistent with drug-induced liver injury secondary to acetaminophen (Figure 4). After the second operation, her clinical condition improved. She had complete resolution of coagulopathy and encephalopathy, and was removed from the liver transplant list. Her renal function improved without hemodialysis, and her oliguria resolved. She was able to tolerate a full diet and was discharged home 20 d after hospitalization. At follow-up three months later, she remains well with normal liver function tests.

DISCUSSION

Over 200 000 weight loss procedures are performed annually in the United States[4]. The Roux-en-Y gastric bypass, first performed in 1966, is the most common bariatric procedure performed in the United States. Internal and incisional hernias are by far the most common cause of bowel obstruction after Roux-en-Y gastric bypass[5].

Small bowel intussusception is a rare cause of bowel obstruction, the etiology of which remains unclear. The incidence of intussusception is approximately 0.1%[6]. The orientation of the intussusceptions is unique in that the distal small bowel, in an anti-peristaltic fashion, is pulled into the jejunojejunostomy. Symptoms may be acute, mimicking a small bowel obstruction, or chronic,

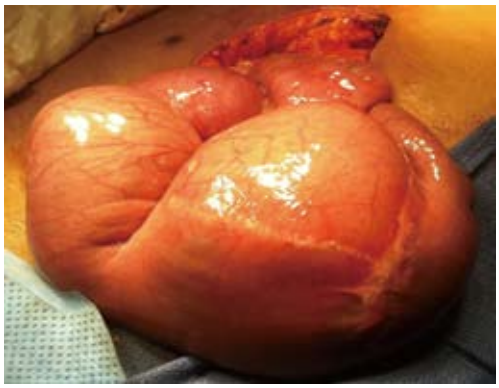

Figure 2 Jejunojejunostomy encountered during exploratory laparotomy.

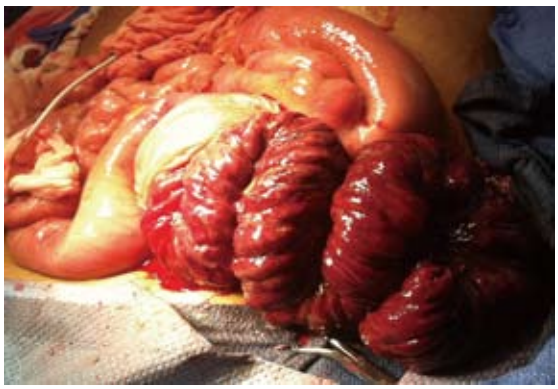

Figure 3 Opened jejunojejunostomy revealed a substantial portion of dead bowel inside it.

with intermittent abdominal pain and nausea. If not recognized and treated promptly, this rare complication may cause obstruction and lead to bowel necrosis. Computerized tomography scan is the diagnostic test of choice, but surgery is sometimes the only way to establish the diagnosis when symptoms are intermittent[7].

This patient's presentation of intussusception was masked by the acute liver failure. A high index of suspicion led to an imaging study that identified her bowel obstruction. Treatment of this condition can range from just the reduction of the small bowel, if the components are viable, with plication of the bowel to prevent recurrence, to a high-risk procedure involving bowel resection and intestinal reconstruction[8].

In conclusion, due to the increasing number of patients who have undergone bariatric surgery, emergency physicians, primary care physicians, general surgeons and gastroenterologists should all be well versed in the varied procedures offered to treat obesity and the potential complications. Surgeons experienced in bariatric surgery should be quickly involved in the management of abdominal complaints in patients with a history of weight loss surgery. This case also highlights the importance of multispecialty collaboration in patients presenting with organ failure in the emergency department. The involvement of the transplant team from the time of admission permitted her to be added to the liver transplant list without delay. Furthermore, the collaboration with the gastroenterologists made it possible to care for this patient optimally, which requires a highly specialized supportive care.

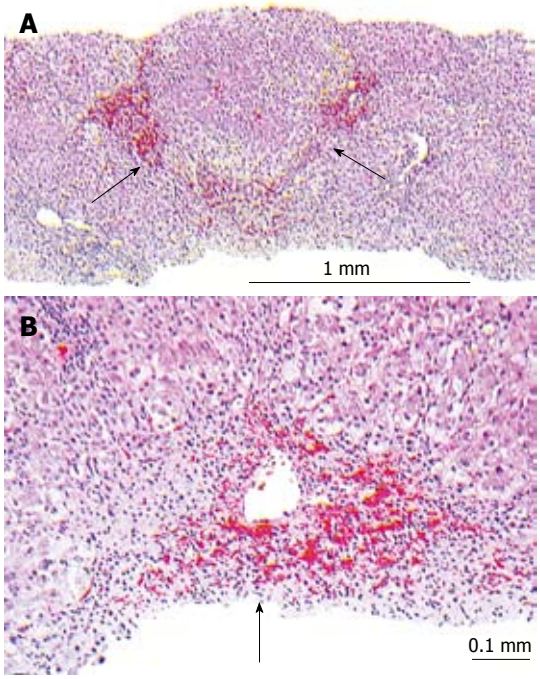

Figure 4 Liver biopsy showing central-central bridging necrosis (arrow) with portal tract sparing (A) and centrilobular necrosis (arrow) (B).

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CASE REPORT

Co-existence of hepatocellular adenoma and focal nodular hyperplasia in a young female

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Abstract

Focal nodular hyperplasia (FNH) and hepatocellular adenoma (HA) are both benign hepatocellular lesions, presenting mainly in women of childbearing age in non-cirrhotic, non-fibrotic livers. Simultaneous occurrence of these two lesions is extremely rare. We herein report a case of a young female without any predisposing risk factors who presented to our emergency department complaining of acute abdominal pain. Imaging studies revealed a 6 cm lesion in the right hepatic lobe and a 2.5 cm lesion in the left hepatic lobe, respectively. In view of the patient's symptoms and lack of a confirmed diagnosis based on imaging, we performed a bisegmentectomy Ⅴ-Ⅵ and a wedge resection of the lesion in segment Ⅲ by laparotomy. Postoperative course was uneventful and the patient was discharged on the fourth postoperative day. The pathology report demonstrated an HA in segments Ⅴ-Ⅵ and FNH in segment Ⅲ, respectively. Six months later, the patient remains asymptomatic with normal liver function tests, ultrasound and magnetic resonance imaging follow-up. To our best knowledge, this is the first case to describe simultaneous occurrence of HA and FNH without the presence of any known risk factors for these entities. The uncertainty in diagnosis and acuteness of presenting symptoms were established criteria for prompt surgical intervention.

Key words: Liver surgery; Liver disease; Hepatocellular adenoma; Focal nodular hyperplasia; Benign hepatic tumor

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INTRODUCTION

Focal nodular hyperplasia (FNH) and hepatocellular adenoma (HA) are both benign nodular hepatocellular lesions, presenting mainly in women of childbearing age in non-cirrhotic, non-fibrotic livers. FNH is the second most common benign hepatic tumor in adults and represents about 8% of all primary hepatic lesions[1]. Typically, FNH is an incidental finding in symptom-free patients. It presents as a palpable abdominal mass in 2% to 4%

of patients, while hepatomegaly and fever occur in less than 1 percent of cases. Spontaneous rupture leading to hemorrhage is extremely rare and there is no incidence of malignant transformation of FNH[2,3]. Levels of serum alpha-fetoprotein are within normal range[4,5].

HA is the third most common benign liver lesion in adults, after hepatic hemangioma and FNH, and is 3 to 10 times less common than FNH[6,7]. A 30 to 40 fold increase in the incidence of HA has been assumed in long term users of oral contraceptives, with a base level incidence of 1 per million in women using oral contraceptives for less than 24 mo or not at all[8,9]. As in FNH, patients with HA are often asymptomatic. Atypical abdominal discomfort is reported in about 30% to 40% of patients and in a small number of cases a palpable mass is present. Large lesions may cause more severe complaints such as abdominal pain; hypovolemic shock after rupture or intratumoral hemorrhage has been observed in some cases. As with FNH, serum alpha-fetoprotein levels are within normal range[4,10].

Simultaneous presence of FNH and HA is very rare and only few cases have been published in the pertinent literature[11-14]. We report a case of a young female without any predisposing risk factors with simultaneous existence of FNH and HA. The diagnostic procedure, therapeutic management and possible pathogenic setting are discussed herein.

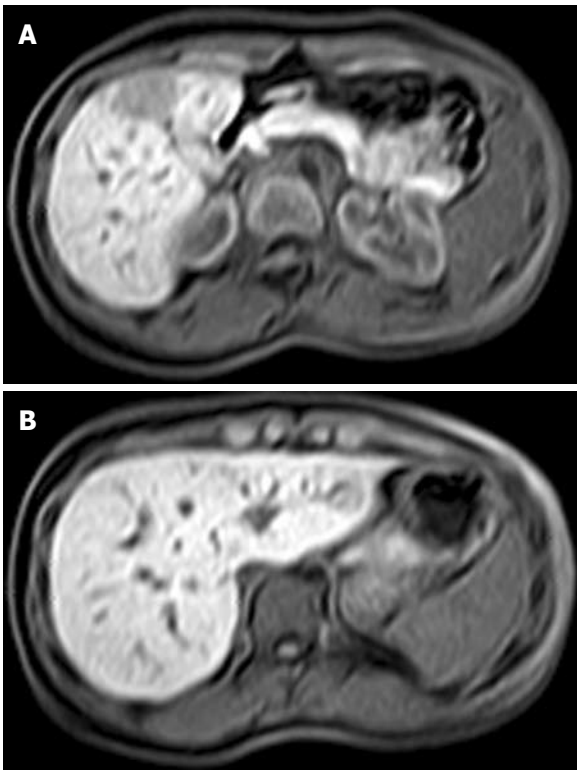

Figure 1 Magnetic resonance imaging of the liver showing a 6 cm lesion in segments Ⅴ and Ⅵ (A) and a smaller lesion of 2.5 cm in segment Ⅲ (B).

CASE REPORT

An 18 year old nulliparous female patient presented to the emergency department complaining of acute abdominal pain. She was 1.65 m tall and weighed about 55 kg upon admission (body mass index 20.2). The patient denied any oral contraceptive pill use, tobacco or alcohol consumption and there was no history of hepatitis. Hepatitis infection markers were negative. Gynecological history was unremarkable, with normal pubertal/postpubertal development and menstruation. Past medical history was likewise unremarkable. The pain was localized in the right upper quadrant of the abdomen and was accompanied by a slight elevation of body temperature (37.2 ℃). The patient did not complain of vomiting, change in bowel habits or any urinary symptoms. Clinical examination did not demonstrate any suspicious signs of high endogenous androgen activity. Routine laboratory studies, including a complete blood count, biochemical profile with liver function tests and α-fetoprotein measurement, were within normal range.

Emergency ultrasound showed a mass of approximately 6 cm in diameter located in the right liver lobe. Upper abdominal magnetic resonance imaging (MRI) revealed a 6 cm lesion in the right liver lobe (segments Ⅴ and Ⅵ) and a smaller one (2.5 cm) in the left lobe (segment Ⅲ), respectively (Figure 1). However, the MRI findings were not specific for the larger lesion in the right lobe (Figure 1A). In view of the patient's symptoms and the lack of a confirmed diagnosis based on preoperative imaging examinations, we opted for prompt surgery.

The patient underwent a bisegmentectomy Ⅴ-Ⅵ and a wedge resection of the lesion in segment Ⅲ by laparotomy. Total operating time was 125 min and blood loss was minimal. Portal triad clamping was not performed at any stage of the operation. Perioperative or postoperative blood or plasma products transfusion was not required. The postoperative course ran uneventfully and the patient was discharged on the fourth postoperative day in good general condition.

Pathology report of the larger lesion in segments Ⅴ and Ⅵ revealed a non-encapsulated hepatocellular neoplasm composed of benign-looking hepatocytes, arranged in sheets and thin cords, occasionally forming rosette-like structures (Figure 2A and B). Isolated arteries were also present. Two different hepatocellular populations were discernible, demonstrating a zonal distribution. In the periphery of the lesion, eosinophilic hepatocytes were present alternately with larger hepatocytes, thus forming a vague lobulation. Abortive portal-tract like structures with thin fibrous septa and mild ductular reaction were observed mainly towards the periphery of the lesion. Overall, the tumor was characterized by mild to moderate steatosis, lipofuscinosis, a well-developed reticulin network, no cytological abnormalities and no inflammatory infiltrates. Immunohistochemical examination showed absence of nuclear expression of beta catenin, while serum amyloid A gave a weak, non-specific reaction. Cytokeratin 7 was positive in the abor-

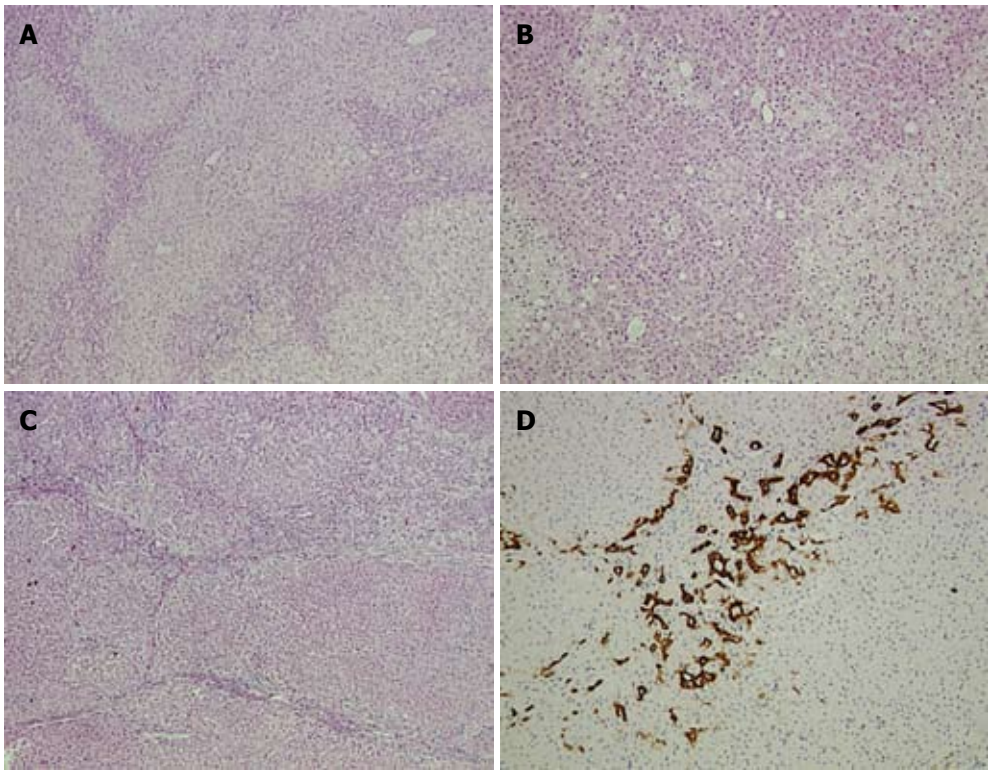

Figure 2 Pathology report of the larger lesion in segments. A, B: Hematoxylin and eosin (HE) staining of the hepatocellular adenoma showing a vague lobularity created by two hepatocytic populations with zonal arrangement. Rosette-like formations are apparent (A ×5, B ×10); C: HE staining of the focal nodular hyperplasia lesion showing nodularity and thin fibrous septa (×5); D: Ductular reaction depicted by cytokeratin 7 expression (×10).

tive bile ducts and ductules and in a few tumor cells at the periphery of the fibrous septa. Cytokeratin 19 was positive only in rare ductular structures. Glutamine synthetase exhibited a patchy positive expression, while L-FABP antibody was not attenuated compared to normal parenchyma. Pathology and immunohistochemistry findings supported the diagnosis of hepatocellular adenoma partly featuring a telangiectatic variant.

The pathology report of the resected segment Ⅲ revealed a non-encapsulated, circumscribed hyperplastic hepatocellular lesion. The tumor was divided into smaller nodules by fibrous septa, which contained dystrophic arteries (Figure 2C). Prominent ductular reaction and mild to moderate inflammatory infiltrates were also observed (Figure 2D). A well developed reticulin network supported the tumoral hepatocytes that showed no cytological atypia and minimal steatosis. The diagnosis was that of focal nodular hyperplasia.

At present, 6 mo after the operation, the patient remains asymptomatic with normal hepatic function tests and ultrasound and MRI imaging show liver regeneration without signs of tumor relapse.

DISCUSSION

We herein describe a case of a young female patient, with no history of oral contraceptive use or other risk factors, exhibiting simultaneous occurrence of FNH and HA in different liver segments.

FNH and HA are two benign liver lesions that very seldom co-exist. The pathogenesis of FNH and HA is considered to be different. On one hand, the exact etiology of FNH is not completely understood. It is generally suggested that FNH originates from arterial malformation, which causes a hyperplastic reaction of normal liver cells to either hyperperfusion or hypoxia[15]. As hyperplastic reactions respond to cell proliferation mechanisms, FNH does not undergo any malignant transformation. Several clinical observations strengthen the above hypothesis as FNH may coexist with hepatic hemangioma or telangiectasia[13,16-19]. Scalori *et al*[20] suggested that cigarette smoking might be an elevated risk index for FNH. On the other hand, HA seems to have a causal relationship with exogenous administration of male and female sex hormones. The use of oral contraceptives provides convincing evidence that the incidence and size of HA is dose and duration dependent[9]. Moreover, the pertinent literature reports sporadic cases of HAs occurring in patients with elevated levels of endogenous androgens, sex hormone imbalance or exogenous administration of androgens as a treatment option for aplastic anemia[12,21-23]. A special form of HA has been described where multiple adenomas occur with at least ten lesions in the liver parenchyma, a condition designated as liver adenomatosis[24]. The etiology of liver adenomatosis is unknown but there is some evidence supporting common pathways with HA[25]. The fact that this condition is often found in women with a history of estrogen exposure could imply that liver adenomatosis is an advanced form of HA. Obesity, positive history of viral hepatitis, alcohol abuse and metabolic diseases, such as Von Gierke glucogen storage disease, have also been depicted as possible risk factors for HA by some authors[26-28].

Recently, a meticulous analysis of a large series of HA by a French collaborative group resulted in their

classification of 4 subtypes[10]. The first group includes heavily steatotic adenomas exhibiting biallelic inactivation of hepatocyte nuclear factor 1 alpha. The second group is characterized by activating mutation of beta catenin and a higher risk for malignant transformation. The third group is defined by the presence of inflammatory infiltrates, sinusoidal dilatation, fibrous septa with ductular reaction and abortive portal tracts, while the fourth group includes adenomas that cannot be classified in any of the above three subtypes. Of note, the newly characterized entity previously called telangiectatic FNH, now believed to be a variant of liver cell adenoma, is classified in the third group of inflammatory/telangiectatic adenomas[29]. The adenoma described herein shared some morphological features with the telangiectatic subtype. However, it was categorized into the fourth group (adenoma not otherwise classified) due to the absence of pathognomonic telangiectatic and inflammatory findings.

It is well established that HA and FNH are two distinct entities with specific histological and molecular features. However, differential diagnosis between them may be difficult in liver resection specimens or liver biopsy-obtained material. It is most likely that in the near future diagnosis will be facilitated by the molecular alterations detected in such lesions. Liver cell adenomas, including subtypes previously called telangiectatic FNH, are monoclonal tumors[26,30]. Conversely, clonal analysis on FNH lesions indicated a monoclonal origin in 14% to 50% of cases, depending on the samples examined and molecular techniques carried out. Furthermore, the mRNA ratio of angiopoietin genes (ANGPT-1 and ANGPT-2, respectively) is found to be attenuated in typical FNH compared to HA[31].

The simultaneous presence of both FNH and HA in the same patient is very rare and only a few cases have been described in the pertinent literature[11-14]. The largest report is the work of a French group that studied the co-existence of benign liver tumors[14]. In this study, HA and FNH were found in the same liver in 5 out of 30 cases with multiple benign liver lesions over a period of 12 years[14]. It is of note that in all cases published in the literature, patients were either on exogenous administration of oral contraceptives or had endogenous elevated sex hormones, conversely to our case presented herein. Laurent *et al*[14] reported that simultaneous occurrence of HA and FNH could be generated secondary to systemic and local angiogenic abnormalities by oral contraceptives, tumor induced growth factors or thrombosis and local arterio-venous shunting.

In our case, the young female patient had no clinical signs of androgen hyperactivity, nor did she receive any oral contraceptives. She did not consume any tobacco or alcohol and her BMI was within normal range. She also had a negative history of viral hepatitis with normal serum hepatitis virus infection assays. Thus, our report is the first in the literature to describe the simultaneous occurrence of HA and FNH without the presence of any known risk factors. In our case, there is no obvious common pathogenic mechanism and the co-existence of the lesions could be incidental. However, the presence of some morphological overlapping features does not exclude the possibility of a commonly shared causative relationship. Deeper knowledge of the molecular background of those two tumors could help recognize the exact association between them.

In recent years, there has been an increased incidence in the diagnosis of FNH and HA. The reason for this fact is increased administration of oral contraceptives on one hand and, on the other hand, imaging modalities evolution. This reality urges the need for providing secure preoperative diagnostic criteria in order to avoid an unnecessary operation and, more importantly, not to skip a necessary resection of a potential malignant tumor in a young or middle aged female. Many imaging modalities are used to diagnose FNH and HA. Especially for FNH, diagnosis can be achieved with high certainty on several imaging studies based on typical features. However, there are atypical imaging findings in both FNH and HA[32]. Sensitivity and specificity of diagnostic imaging has been improved for the diagnosis of FNH, while the gold standard for HA is still liver biopsy. In our case, we decided to proceed to surgery mainly due to preoperative diagnostic uncertainty and acute symptomatology.

In this report, we present a case of a young female patient with co-existence of FNH and HA of the liver without any previous exogenous administration of oral contraceptives or any other known risk factors predisposing to these liver lesions. This fact, together with the absence of typical radiological characteristics, could imply a common pathway in the pathogenesis of these two benign liver lesions or the presence of an intermediate form with interesting radiological, molecular or pathological features. The uncertainty in diagnosis and acuteness of presenting symptoms were established criteria for prompt surgical management. However, in cases of diagnosed benign tumors, surgery should be performed only when tumors are symptomatic or have a risk of complications such as hemorrhage, rupture or malignant potential.

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CASE REPORT

Liver abscess after implantation of dental prosthesis

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Abstract

Pyogenic liver abscesses are rare but a life-threatening important condition. Dental procedures constitute only rare cases of pyogenic liver abscesses, with only a few cases in the literature. We report a patient with liver abscess following a dental procedure. A 74 years old diabetic male patient was admitted to our hospital with complaints of fatigue, 40 ℃ fever, rigors and right upper quadrant pain, 3-4 d after a dental procedure. Physical examination revealed fever and tenderness in the right upper quadrant. Laboratory examination revealed leucocytosis, elevated erythrocyte sedimentation rate and C-reactive protein and moderately elevated transaminases. An abscess was detected in radiological examination in the medial part of the left lobe of liver, neighboring the gall bladder. He was successfully treated with percutaneous abscess drainage and antibiotherapy.

Key words: Liver abscess; Dental procedures; Bacteremia; Immunosuppression; Abscess treatment

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INTRODUCTION

Pyogenic liver abscesses are uncommon but a life-threatening important condition. Pyogenic liver abscesses are caused by infections, usually originating from biliary or portal pathologies, gastrointestinal and subdiaphragmatic infections, traumas, sepsis (hematogenous route) or idiopathic.

Dental procedures and diseases are very rare etiologies of pyogenic liver abscesses and, to date, only a few cases of pyogenic liver abscess associated with dental procedures have been reported in the literature[1-5]. A case of hepatic abscess has also been reported that originated from the oral cavity other than dental diseases[6].

We report a patient with liver abscess following a dental procedure (implantation).

CASE REPORT

A 74 years old man underwent a dental prosthesis implantation approximately ten days ago. Three to four days after the dental prosthesis implantation, he suffered from malaise, abdominal pain in right upper quadrant and chills. He recoursed to the first medical center with 40 ℃ fever and increasing complaints. In the first hospital, liver abscess was suspected on ultrasonographic (USG) evaluation of the abdomen and with USG-guided drainage, this abscess material was sent for cultural analysis simultaneously with the blood culture. Intravenous empirical antibiotherapy with Ceftriaxone 1 gr *bid* + Metronidazole 500 mg *bid* was given in the first medical center. The patient recoursed to our center for treatment by his own desire.

He had a 3 years history of diabetes mellitus and used

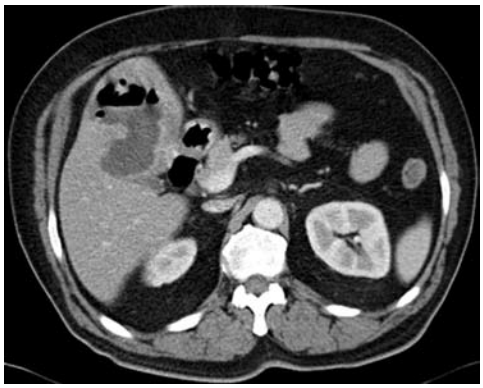

Figure 1 An intraparenchymal abscess approximately 82 mm × 73 mm in diameter including air-fluid level viewed within the medial of the left lobe in liver in abdominal computed tomography.

metformin irregularly. Physical examination revealed weakness, a blood pressure of 120/80 mmHg, a heart rate of 84 beats/min and a body temperature of 38.7 ℃. His conjunctiva were pale. Tenderness was found in the right upper quadrant and other physical findings were unremarkable.

Laboratory examination revealed the following findings: hemoglobin was 11.2 g/dL; white blood cell count was 11.200 cells/mm^3 with 87.6% neutrophils; serum transaminases and prothrombin time were mildly elevated; serum total bilirubin, alkaline phosphatase and gamma-glutamyl transferase levels were all within normal range; serum glucose was 256 mg/dL; glucosylated hemoglobin level was 6.8%; erythrocyte sedimentation rate was 69 mm/h; C-reactive protein level was 115 mg/L; serological tests for infection with hepatitis B, C, human immunodeficiency virus, brucella, salmonella and amebiasis were all negative; and urine analysis was unremarkable except for microalbuminuria. Chest radiograph was normal.

Ultrasonography of the abdomen revealed that the liver was steatotic and there was a single hypoechoic-heterogenous lesion 75 mm × 60 mm in diameter within the medial part of the left lobe, neighboring the gall bladder. Abdominal computed tomography (CT) scan showed no contrast involvement in the lesion after the contrast injection but showed involvement just around this lesion (Figure 1). Separately, the cortical cyst 10 mm in diameter was detected on the left kidney. Calibration of small and large intestinal segments and wall thickness were normal. Gall bladder and biliary tract were normal. No intraabdominal fluid collection was detected.

After diagnosis of liver abscess, the patient was treated with intravenous Imipenem 4 mg × 500 mg + Metronidazol 3 mg × 500 mg empirically. Hydration and subcutaneus insulin injections were applied. We learned that streptococcus subspecies was isolated from the abscess material culture and from the blood sample taken before empirical antibiotherapy. Urine culture was negative.

After that, USG-guided percutaneous drainage of the liver abscess was performed. A total of 400 mL foul-smelling purulent material was drained; 300 mL on the first day and 100 mL on the following day. His complaints improved after the drainage of the abscess and 14 d of antibiotherapy. The fever decreased, he was clinically well and the white blood cell count, CRP and sedimentation rate values returned to normal.

Control USG evaluation after 14 d showed almost complete resolution of the liver abscess. Levofloxacin 500 mg/d po for seven days was recommended after discharge from hospital.

In our case we demonstrated a liver abscess development with hematogenous route due to the dental procedure. Isolating the same microorganisms from both the blood sample and abscess material, the onset of his symptoms 3-4 d after the dental prosthesis implantation and no detection of another infection origin supported our opinion. This procedure might have caused bacteremia spreading to the liver *via* the hepatic artery.

DISCUSSION

Isolated pathogens from a liver abscess are usually gram negative bacterias like *Escherichia Coli*, *Klebsiella*, *Pseudomonas*; gram positive microorganisms like *Streptococcus* and *Staphylococcus* species; and anaerobic organisms like *Fusibacterium*, *Bacteroides*, *Ameobas* or *fungal microorganisms*[1].

Prognosis may be poor if diagnosis and treatment are delayed in pyogenic liver abscesses. CT scan and ultrasound-guided drainage of pyogenic liver abscesses are safe and effective methods of treatment[7]. Liver transplantation, diabetes and a history of malignancy are risk factors for pyogenic liver abscess[8].

Dental diseases or procedures are very rare etiological factors of liver abscesses. However, poor oral hygiene might also be an independent risk factor. Usually hematogenous spread of bacteria occurs after interventional treatment of dental disease.

Patients with increased risk of infection, such as immunosuppression, diabetes and malignancy, should be treated with prophylactic antibiotherapy during and after dental procedures. Appropriate oral care is clearly important, not only for dental, but also for systemic diseases.

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CASE REPORT

Hepatocellular adenoma associated with familial adenomatous polyposis coli

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Author contributions: Inaba K and Sakaguchi T treated the patient and wrote the manuscript; Kurachi K and Nakamura T treated the patient and helped to draft the report; Takehara Y reviewed the radiological features of the case; Tao H and Maekawa M examined the genetic alterations; Mori H, Baba S and Sugimura H contributed to the pathological examination and decided the final pathological diagnosis; Konno H was responsible for the patient management and supervised and approved the final manuscript.
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Abstract

Hepatocellular adenoma (HCA) is a benign liver tumor that most frequently occurs in young women using oral contraceptives. We report a rare case of HCA in a 29 years old female with familial adenomatous polyposis (FAP). The first proband was her sister, who underwent a total colectomy and was genetically diagnosed as FAP. A tumor, 3.0 cm in diameter, was detected in the right lobe of the liver during a screening study for FAP. A colonoscopy and gastroendoscopy revealed numerous adenomatous polyps without carcinoma. The patient underwent a total colectomy and ileo-anal anastomosis and hepatic posterior sectoriectomy. The pathological findings of the liver tumor were compatible with HCA. The resected specimen of the colon revealed multiple colonic adenomatous polyps. Examination of genetic alteration revealed a germ-line mutation of the adenomatous polyposis coli (*APC*) gene. Inactivation of the second *APC* allele was not found. Other genetic alterations in the *hepatocyte nuclear factor 1 alpha* and *β-catenin* gene, which are reported to be associated with HCA, were not detected. Although FAP is reported to be complicated with various neoplasias in extracolic organs, only six cases of HCA associated with FAP, including the present case, have been reported. Additional reports will establish the precise mechanisms of HCA development in FAP patients.

Key words: Hepatic adenoma; Familial adenomatous polyposis coli; Extrahepatic manifestation; Adenomatous polyposis coli gene; Hepatocyte nuclear factor 1 alpha

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INTRODUCTION

Hepatocellular adenoma (HCA) is a benign liver tumor that usually arises in women who are over 30 years old and have used oral contraceptives for over 5 years[1]. Other risk factors associated with HCA have been described, including glycogen-storage diseases, androgens, anabolic steroids, diabetes mellitus, some drugs and pregnancy[2-5].

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disease caused by a mutation in the adenomatous polyposis coli (*APC*) gene. FAP is characterized by the early onset of multiple colorectal adenomatous polyps, with an inevitable progression to carcinoma if left untreated. Additionally, FAP is known to be associated with extracolic neoplasms in various other organs; adenomas and carcinomas of the upper gastrointestinal tract, desmoid tumors and thyroid carcinomas[6]. Due to familial screening and prophylactic colectomies, the prognosis of FAP patients has improved[6-8]. Thus, extracolic tumors have become more important causes of mortality[7]. Duodenal or periampullary cancer and desmoids are the two main causes of mortality after a total colectomy[9]. Other rare extracolic manifestations include cancers of the thyroid, liver, bile ducts and central nervous system[6,7,9]. HCA is rare for FAP-associated extracolic neoplasms[10].

Herein, we report a rare case of HCA concomitant with FAP. She had no history of oral contraceptive use or other risk factors for HCA. We summarize previous case reports[5,10-14] and consider HCA arising in FAP patients.

CASE REPORT

A 29 years old Japanese woman was called for familial surveillance of FAP because her 27 years old sister had undergone a total colectomy due to the diagnosis of ascending colon cancer arising from FAP, already confirmed by gene analysis. Her 46 years old father died of gastric cancer but FAP was uncertain. Her son had suffered from hepatoblastoma which had been resected when he was 18 mo old. Her preoperative clinical laboratory tests, including liver function, were normal. Serologically, serum hepatitis B and hepatitis C virus markers were negative. Serum levels of alpha-fetoprotein and des-γ-carboxy prothrombin were also within normal ranges. Preoperative computed tomography (CT) showed a tumor in the posterior sector of the right lobe, measuring 28 mm in diameter. The tumor showed a slight inhomogeneous low density area on the unenhanced scan when compared with the surrounding liver parenchyma (Figure 1). The tumor was well enhanced in the early phase after the contrast medium injection. The tumor became indistinguishable in the late phase. Although the tumor was not detectable on T1-weighted magnetic resonance imaging (MRI), it was detected as a mild hyper-intense tumor in the posterior sector on T2-weighted MRI (Figure 1). The tumor was indiscernible in the arterial phase, but became a hypo-intense area in the hepato-biliary phase after gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid enhancement on T1-weighted MRI. No obvious

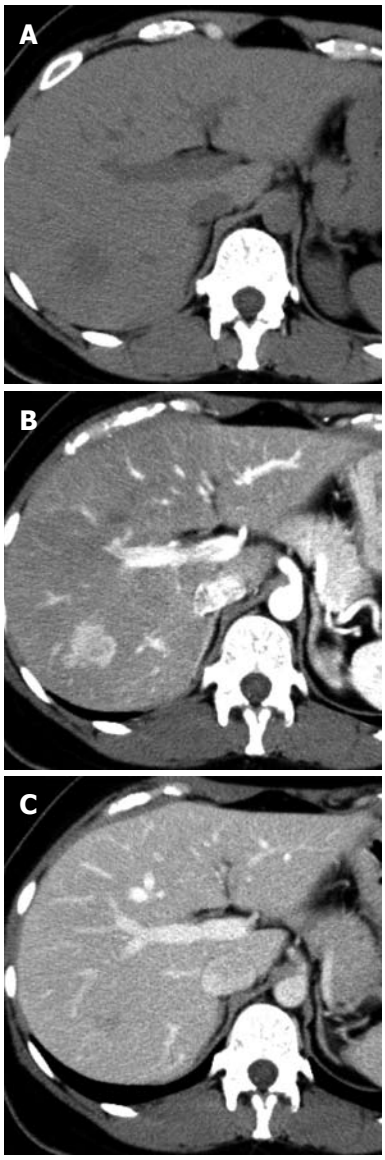

Figure 1 Preoperative computed tomography scan revealed a 28 mm tumor in the posterior sector of the right hepatic lobe. A: Plain computed tomography showed a tumor as a slight low density area; B: The tumor was inhomogeneously enhanced with a ragged border during the early phase; C: The tumor was indistinguishable in the late phase.

capsular formation or visible central scars were observed (Figure 2). Hepatic arteriography showed a tumor stain without any abnormalities in vascular structure or angioplany. A total colonoscopy revealed numerous polyps of various sizes throughout the colon and rectum but no obvious colorectal carcinoma was found. Gastroendoscopy also found thick polyps without carcinoma.

On the basis of clinical features[15] and previous literature[10-13], we performed a total colectomy and ileoanal anastomosis and hepatic posterior sectoriectomy on December 2008. Macroscopically, numerous polyps of various sizes, including one lateral spreading tumor in the ascending colon, were found in the mucosal surface of the resected colon specimen. In the cut surface of the resected liver specimen, the tumor grossly showed a faint yellow tumor without hemorrhage or necrosis. The

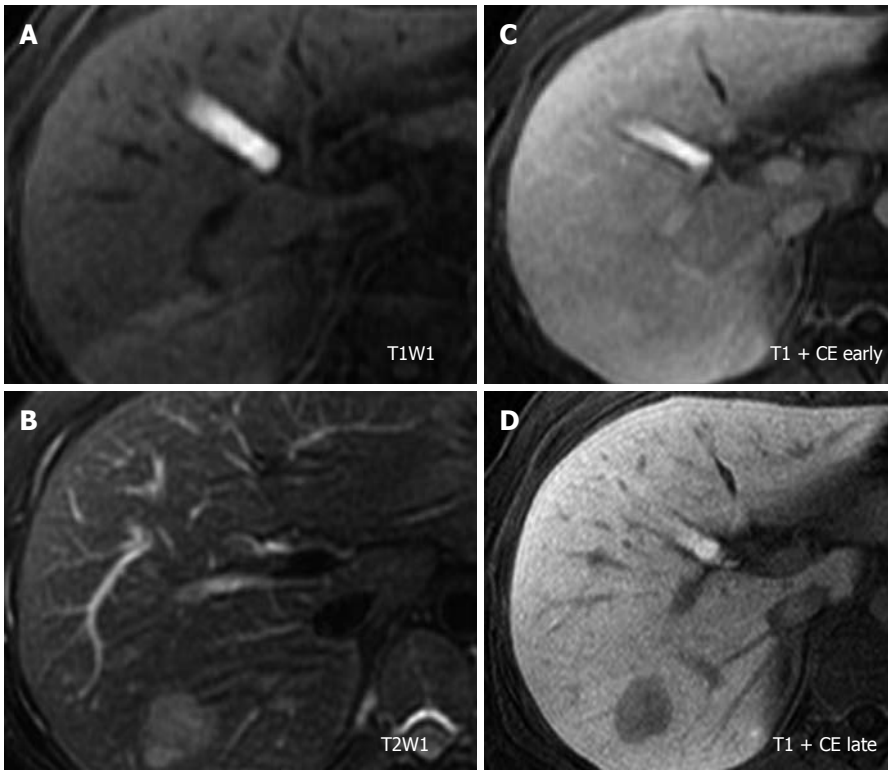

Figure 2 Magnetic resonance imaging of the tumor. A: The tumor showed an iso-intensity with the surrounding liver parenchyma on T1-weighted imaging; B: The tumor was visualized as a heterogeneous hyper-intense mass on T2-weighted imaging; C and D: After gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid enhancement, the tumor was discernible in the arterial phase and was clearly detected as a hypo-intense lesion in the hepato-biliary phase on T1-weighted imaging. CE: Contrast enhanced.

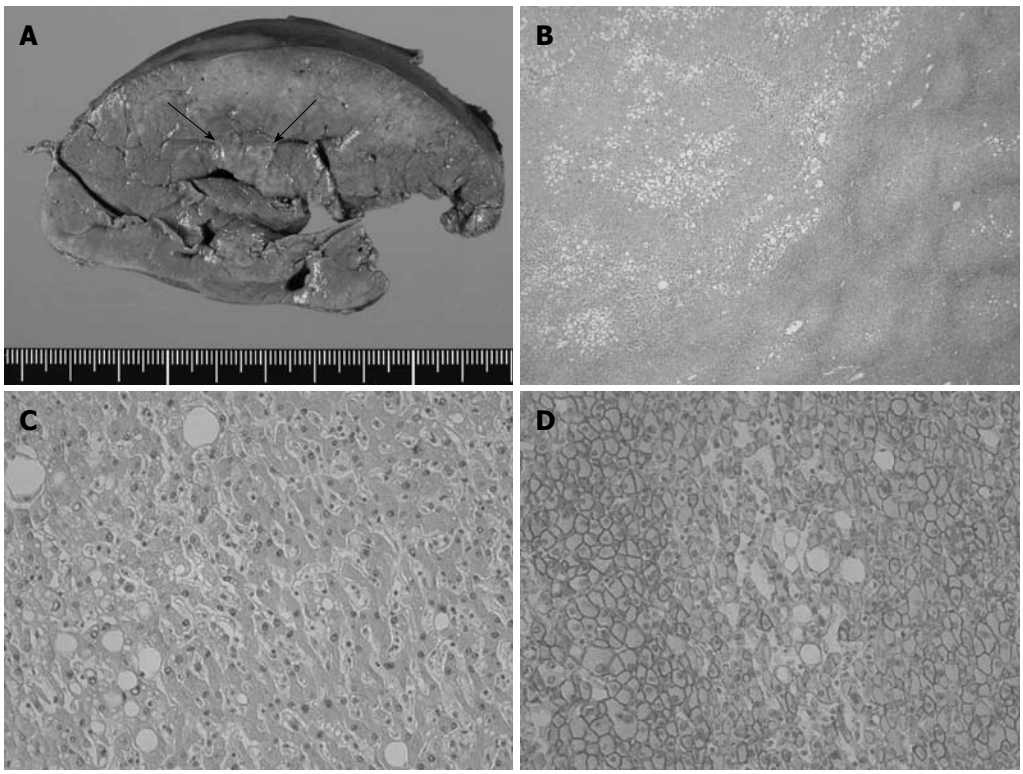

Figure 3 Pathological findings of the liver tumor. A: Cut surface of formalin-fixed liver specimen. The tumor was unencapsulated and its border was ill-defined (arrow); B, C: Microscopically, the tumor consisted of low-grade atypical hepatocytes, without cellular mitosis or changes in cellular density and structures. Fatty deposition in the tumor cells was ubiquitously remarkable. Neither biliary structures nor portal triads were present within the tumor (hematoxylin-eosin stain, original magnification ×40 in B and ×200 in C); D: β-catenin was immunohistochemically detected on the cytomembrane. Neither aberrant nuclear nor cytoplasmic accumulations were found (original magnification ×100).

tumor showed an ill-defined border and was unencapsulated (Figure 3A). The surrounding liver tissue seemed to be normal parenchyma.

Histologically, multiple colorectal polyps were adenomas with mild to moderate cellular atypia. A lateral spreading tumor was a tubular adenoma with severe atypia. The liver tumor consisted of low-grade atypical hepatocytes, without cellular mitosis or changes in cellular density and structures. Fatty deposition in the tumor cells was remarkable in some parts. No biliary structures or portal triads were present within the tumor (Figure 3B and C). There was no underlying hepatitis, fibrosis or cirrhosis in the adjacent liver parenchyma. These pathological findings were compatible for hepatic adenoma. To clarify the pathogen-

Table 1 Reported cases of primary hepatocellular adenoma associated with familial adenomatous polyposis

Case	Age/gender	Location	No. of tumors	Size (cm)	Treatment	Oral contraception	Steroid use	Mutated codon in the *APC* gene	Disorder in the somatic gene of HCA
Bala *et al*[11]	2/F	Right lobe	Solitary	10	Resection	(-)	(-)	1451	Loss of wild-type allele of *APC*, mutation of *p53*
Nakao *et al*[13]	20/F	Left lobe	Multiple	5.5	Observation	(-)	(+)	ND	ND
Bläker *et al*[10]	27/F	ND	ND	ND	ND	ND	ND	1156	1516
Jeannot *et al*[12]	37/F	Right lobe	Solitary	7	Resection	(+)	(-)	1062	Mutation of *HNF1α*
Okamura *et al*[5]	27/M	Left lobe	Solitary	8.5	Resection	(-)	(-)	ND	ND
[1]Toiyama *et al*[14]	25/M	Left lobe	Solitary	5.5	Resection	(-)	(-)	ND	Mutation of *HNF1α*
This case	29/F	Right lobe	Solitary	3	Resection	(-)	(-)	499	(-)

[1]Case 6 is hepatocellular carcinoma within hepatocellular adenoma (HCA) in a familial adenomatous polyposis patient. *APC*: Adenomatous polyposis coli; ND: Not described; *HNF1α*: Hepatic nuclear factor 1 alpha; F: Female; M: Male.

esis of this patient, genetic alterations of the germ-line and somatic genes were examined[16]. Sequencing of the germ-line *APC* gene revealed a transition from ACG to ATG at codon 499 in exon 11. No loss of the *APC* gene in HCA cells was demonstrated by fluorescence in situ hybridization (data not shown). No additional somatic mutation of the *APC* gene was found in the HCA. Moreover, a mutation of the hepatocyte nuclear factor 1 alpha (*HNF1* gene, which is reported to be related to HCA[12]) was not detected.

The postoperative course was uneventful without any complications, and the patient was discharged twenty days after the operation. Follow-up CT scans revealed no signs of recurrence and other abdominal extracolic lesions 3 years after surgery.

DISCUSSION

HCA is usually found in healthy young women, especially those who use oral contraceptives for a long time. More than 750 HCA cases have been reported since the first report, showing a possible etiological association between HCA and contraceptives[17]. Glycogen-storage diseases, androgens, anabolic steroids, diabetes mellitus, some drugs and pregnancy have been reported as other causal factors for HCA[2-5]. However, the present patient did not have any known exogenous or endogenous pathogenic factors, except for FAP.

Patients with FAP can develop extracolonic lesions such as desmoid tumors, adenomas and carcinomas of the upper gastrointestinal tract[6]. An increased risk of hepatic tumors, mainly hepatoblastoma and hepatocellular carcinoma[18-20], has also been shown in FAP patients. Hepatoblastomas develop in young patients with FAP at least 100 times more frequently than in the general population[18]. Kurahashi *et al*[19] reported a biallelic mutation in the *APC* gene in hepatoblastoma developed in a FAP patient showing a germline mutation in *APC*. In fact, this patient's son had hepatoblastoma at the age of 18 mo but the precise genetic information of hepatoblastoma has not been obtained.

Reported cases of HCAs arising in FAP patients are extremely rare. According to our literature review, only seven cases, including our case, have been reported (Table 1)[5,10-14]. Five of these patients were female and two were male. Among them, one patient used oral contraceptives[12] and another had a medical history of androgenic steroid use for the treatment of anaplastic anemia[13]. HCA containing HCC in a male FAP patient was recently presented[14].

The germ-line mutation of the *APC* gene was examined in four cases, including our patient[10-12]. Bala *et al*[11] suggested that inherited mutations in the *APC* gene between codon 1444 and 1578 significantly increase the risk of developing extraintestinal tumors, including liver tumors. However, the other *APC* gene mutation occurred at different codons in 3 cases[10,12], including the present case (Table 1). Biallelic inactivation of the *APC* gene was described in two cases[10,11] (Table 1). In the first case, loss of the wild-type *APC* allele, which caused hemizygosity of the inherited mutation, was demonstrated[11]. A somatic 4-bp insertion was detected at codon 1516 in another case[10]. These findings suggest that the relationship between the *APC* gene anomaly and HCA is more complicated than initially expected.

Recently, genotype/phenotype classifications of HCA have drawn attention as a noticeable phenomenon from the aspects of pathogenesis and pathological tumorigenesis[21-23]. In their reports, HCAs are classified into four categories: (1) HCAs with mutations of the *HNF1* gene (H-HCA, 35%-40%); (2) HCAs with mutations of the *β-catenin* gene (β-HCA, 10%-15%); (3) inflammatory HCAs with mutation of the *IL6ST* gene (I-HCA, 40%-50%); and (4) HCAs without markers (unclassified HCA, less than 5%-10%). Our patient showed no symptoms or signs of an inflammatory syndrome. Additionally, the HCA in the present case morphologically lacked the typical characteristics of I-HCA, such as inflammatory infiltrates, sinusoidal dilatation and numerous thick arteries[21-23]. The *β-catenin* gene was supposed to be normal[24,25] because *β-catenin* was immunohistochemically detected only around the cytomembrane, without aberrant nuclear and cytoplasmic staining distributed in random and heterogeneous patterns (Figure 3D). Thus, the tumor is not β-HCA. In our case, histopathological characteristics of the liver tumor were closely compatible for H-HCA (Figure 3B and C) since H-HCAs are pathologically characterized by marked lipid deposition in tumor cells without

cytological abnormalities or inflammatory infiltrates[21-23]. However, no *HNF1* gene mutation was identified (data not shown). Although this tumor may be categorized as an unclassified HCA, further investigation of tumorigenesis is necessary[26].

In conclusion, we reported here a rare case of HCA arising in a female FAP patient. Because of its rarity, the pathogenesis of HCAs in patients with FAP remains undefined. More cases should be examined to establish the genetic alterations associated with benign hepatic tumorigenesis in FAP patients. Results may shed light on a breakthrough for hepatocellular carcinogenesis[25].

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Miami, FL, United States

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

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

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

February 16-19, 2012
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Taipei, Taiwan, China

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

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

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

April 18-22, 2012
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Barcelona, Spain

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

May 16-19, 2012
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San Francisco, CA, United States

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Acknowledgments

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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]

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

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

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

Patent (list all authors)

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

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

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

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