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G. 知的所有権の取得状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

厚生労働科学研究費補助金（難病・がん等の疾患分野の医療の実用化研究事業（肝炎関係研究分野））
総合分担研究報告書

肝発癌例と非発癌例での血中 WFA+-M2BP と WFA+-CSF1R の検討
－発癌 3 年前の血清マーカーからの検討－

熊田 卓　大垣市民病院・副院長

研究要旨：2000 年 1 月から 2009 年 12 月の間に経験した B 型肝炎ウイルス（HBV）キャリアもしくは C 型肝炎ウイルス（HCV）キャリア 2750 例中、3 年以上経過観察されかつ血清保存された 1110 例で経過観察中に 83 例の肝細胞癌（HCC）が発生した。この発癌例の 83 例と非発生例の 1027 例で年齢、性、成因（HBV もしくは HCV）、Child-Pugh 分類、血小板、alanine aminotrasnsferase（ALT）の 6 因子をを propensity score 法でマッチさせて発癌例 79 例、非発癌例 79 を抽出した。これらの症例ので HCC 診断時（非発癌例では最終血清保存日）、1 年前、2 年前、3 年前の保存血清で *Wisteria floribunda* agglutinin-reactive 90 K/Mac-2 binding protein（WFA+-M2BP）と WFA+-colony-stimulating factor 1 receptor（CSF1R）、α-fetoprotein（AFP）、lens culinaris agglutinin A-reactive α-fetoprotein（AFP-L3%）、DCP（des-gamma-carboxy prothrombin）、FIB4 index、AST-to-platelet ratio index（APRI）を測定した。HCC 診断前 3 年前の血清で ROC（Receiver Operatorating Characteristic）曲線を作成すると AUC（Area under the curve）は WFA+-CSF1R（0.7250）で最も高く、次いで AFP（0.6599）、FIB4 index（0.6192）、WFA+-M2BP（0.6057）、APRI（0.5905）、AFP-L3%（0.5685）、DCP（0.4903）の順であった。WFA+-CSF1R 及び WFA+-M2BP は経過観察を行った 3 年間の経時的変化間認められなかったが、経過観察開始時（3 年前）で高値を示す症例は肝発癌の可能性が高く、特に WFA+-CSF1R は高発癌状態の良いマーカーとなりうる可能性が示された。

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A. 研究目的

肝細胞癌（HCC）診断に腫瘍マーカーとして、α-fetoprotein（AFP）、lens culinaris agglutinin A-reactive α-fetoprotein（AFP-L3%）および DCP（des-gamma-carboxy prothrombin あるいは protein induced vitamin K absence-Ⅱ：PIVKAⅡ）の 3 種類が良く用いられている。2009 年 4 月からは AFP と DCP の 2 つの腫瘍マーカーの同時測定が保険診療上認められ、肝癌診療ガイドライン（2009 年版）にも、対象者を高危険群（B 型慢性肝炎、C 型慢性肝炎、肝硬変）と超高危険群（B 型肝硬変、C 型肝硬変）に分け、前者では 6 ヶ月に一度の超音波検査と腫瘍マーカー（AFP と AFP-L3% と DCP）の測定を、後者では 3-4 ヶ月毎の超音

波検査と腫瘍マーカーの測定に加え6-12ヶ月毎のCT/MRI検査（Option）が推奨されている。

一方、HCCは線維化の進行した例から発生しやすいことが知られており、線維化を正確に、非浸襲的に測定する方法が求められている。今回我々は線維化マーカーとして開発された血清中の90 K/Mac-2 binding protein (M2BP) 及びmacrophage colony-stimulating factor 1 receptor (CSF1R) を測定する機会を得て、保存血清を用いて肝発癌例、非発癌例で *Wisteria floribunda* agglutinin-reactive (WFA^+) - M2BP及びWFA^+-CSF1Rを測定し、その臨床的意義について検討した。

B. 研究方法

B型肝炎ウイルス（HBV）キャリアもしくはC型肝炎ウイルス（HCV）キャリア2750例中、(1) HBs抗原もしくはHCV抗体が6カ月以上陽性、(2) HCC診断前3年以上経過観察されている、(3) 血清が12カ月の間隔で少なくとも2点以上で保存されている、(4) 発癌例では最大腫瘍径3cm以下3個以下で診断されている、(5) ワーファリンが内服していない5点を満たす1110例を対象とした。経過観察中に83例で発癌が認められた。

この発癌83例と非発癌1027例を年齢、性、成因（HBVもしくはHCV）、Child-Pugh分類、血小板、alanine aminotrasnsferase (ALT) の5因子をpropensity score法を用いてマッチさせたところ、発癌群79例、非発癌群79例が抽出された。これらの症例でHCC診断時（非発癌例では最終血清保存日）、1年前、2年前、3年前の保存血清でWFA^+- M2BP 、WFA^+-CSF1R 、AFP、高感度AFP-L3%（μTAS Wako i30）、DCPを測定した。また、3年前の血液データからFiB-4 = [年齢 (y) × AST (IU/L)]/ [血小板 (10^9/L) × ALT (IU/L) $^{1/2}$]、AST-to-platelet ratio index (APRI) = [{AST (IU/l) / ALT_ULN (IU/l)} × 100]/ platelet count (10^9/L) も測定した。

C. 研究結果

(1) 背景因子

表1、発癌群と非発癌群の背景因子（3年前）

	Characteristics	HCC (n=79)	Non-HCC (n=79)	P
Age	Median (Range)	67 (34-84)	67 (14-84)	0.692
Gender	Male / Female	49/ 30	45/ 34	0.517
Etiology	B / C / B+C	13/65/1	11/67/1	0.906
Child-Pugh classification	A / B / C	63/13/3	67/10/2	0.699
ALT(IU/L)	Median (Range)	49(7-361)	49 (12-321)	0.900
Platelet ($x10^9$/mL)	Median (Range)	99 (32-340)	122(21-414)	0.124
Presence of cirrhosis	Present/Absent	63/16	64/15	0.8412
WFA^+-CSF1R (ng/mL)	Median (Range)	224.6(33.1-785.8)	135.2 (52.7-638.0)	<0.001
WFA^+-M2BP (ng/mL)	Median (Range)	6.92(0.48-26.29)	3.67(0.2-31.46)	0.0135
AFP (ng/mL)	Median (Range)	11 (0.8-627.1)	5.7(0.8-1131.4)	<0.001
AFP-L3 (%)	Median (Range)	5.0(0.00-11.6)	4.2 (0.5-10.3)	0.1446
DCP (mAU/mL)	Median (Range)	15 (5-304)	14 (5-324)	0.6735
Tumor size(cm)	Median (Range)	1.8 (1.0-3.0)	NA	NA
Tumor number	Single / Multiple	53/26	NA	NA
TNM stage	I / II / III	36/30/13	NA	NA

表1に経過観察開始時（3年前）の発癌群79例と非発癌群79例の背景因子を示す。年齢、性、成因、Child-Pugh分類、ALT、血小板に差は認めていない。HCC診断時の最大径は1.8cm (1.0-3.0cm)、単発53例、多発26例、stageはⅠが36例、Ⅱが30例、Ⅲが13例であった。WFA^+-CSF1Rは発癌群では非発癌群に比し有意に高値であった（P<0.001）。一方、WFA^+-M2BPも有意に高値であった（P=0.0135）。

(2) AFPの経時的変化

AFPは発癌1年前までの変化は乏しく、診断時に上昇する例が多く（図1）、診断時には1年前に比し有意の上昇を認めた（P<0.0001、表2）。

図1、AFPの変化

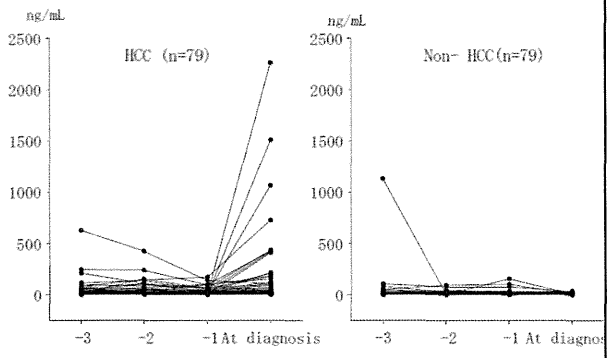

表2、各種マーカーの変化

Biomarker	3年前と2年前	2年前と1年前	1年前と診断時
WFA+-CSF1R	P=0.1208	P=0.4709	P=0.5933
WFA+-M2BP	P=0.0703	P=0.9606	P=0.7519
AFP	P=0.9315	P=0.1811	P=0.0006
AFP-L3%	P=0.7475	P=0.0009	P<0.0001
DCP	P=0.1542	P=0.7519	P<0.0001

(Wilcoxon paired rank sum test)

(3) AFP-L3%の経時的変化

AFP-L3%は診断1年前および診断時に上昇する症例を多く認めた（図2）。診断1年前と2年前および診断1年前と診断時の変化が有意であった（P=0.0009および<0.0001、表2）。

(4) DCPの経時的変化

DCPは発癌1年前までの変化は乏しく、診断時に上昇する例が多く（図1）、診断時には1年前に比し有意の上昇を認めた（P<0.0001、表2）。

(5) WFA+-M2BPの経時的変化

WFA+-M2BPは癌発見時の値を含め3年前、2年前1年前の変化は認められなかった（図4、表2）。

(6) WFA+-CSF1Rの経時的変化

WFA+-CSF1Rも同様に、癌発見時の値を含め3年前、2年前1年前の変化は認められなかった（図5、表2）。

(7) 発癌3年前の各種マーカーのROC曲線

3年前の各種マーカーのAUCを求めるとWFA+-CSF1Rが0.7250 (0.6246-0.8069) で最も高く、次いでAFP 0.6626 (0.5700-0.7442)、FIB-4 index 0.6192 (0.5234-0.7066)、WFA+-M2BP 6050 (0.5015-0.6936)、APRI 0.5905 (0.4957-0.6791)、AFP-L3% 0.5685 (0.4755-0.6568)、DCP 0.4903 (0.3970-0.5844) の順であった。WFA+-CSF1RのAUCはFIB-4 index、WFA+-M2BP、APRI、AFP-L3%、DCPに比し有意に高値であった。また、AFPのAUCはAFP-L3%、DCPに比し有意に高値であった。

図2、AFP-L3%の変化

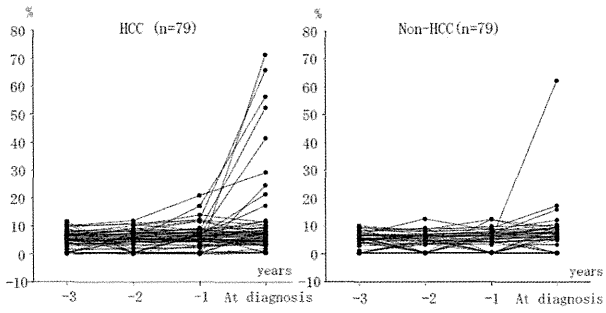

図3、DCPの変化

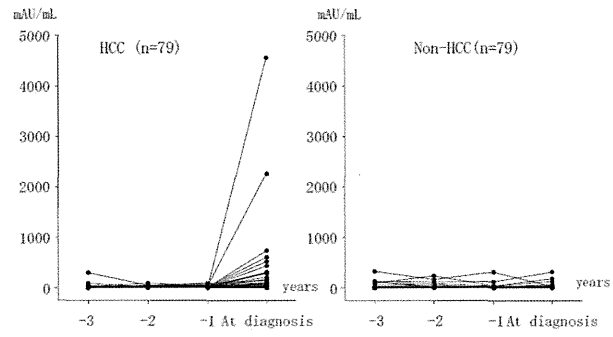

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図4、WFA+-M2BPの変化

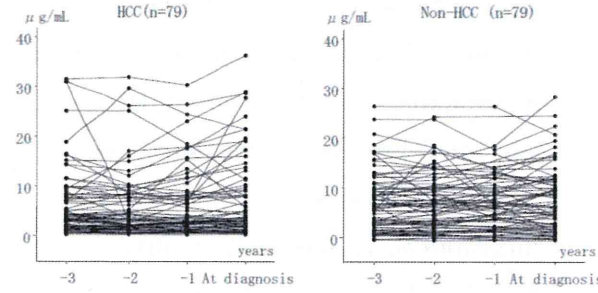

図5、WFA+-CSF1Rの変化

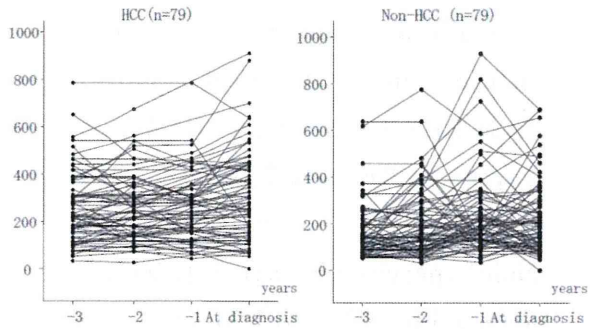

図6、各種マーカーのAUC(3年前)

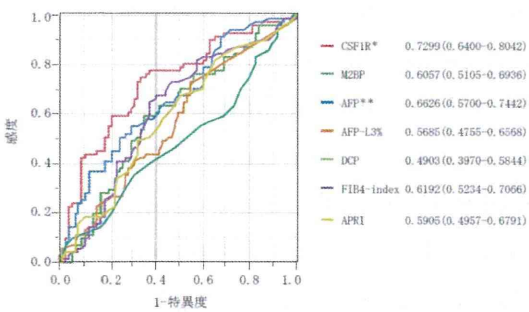

表4　HCCを疑いMRIのきっかけとなった理由と高感度AFP-L3分画

Triggers to perform MRI	n	hs-AFP-L3 >7% at -1 year	hs-AFP-L3 >7% at diagnosis
(a) Ultrasound	86	29.6%	36.0%
Increase of the tumor number	51	27.7%	39.2%
Increase of the tumor size	18	16.7%	11.1%
Change of the echo pattern in nodules	17	50.0%	52.9%
(b) Biomarkers	5	80.0%	60.0%
(c) Others	13	46.2%	53.8%

D. 結論

背景因子を合わせた肝発癌群 79 例と非発癌群 79 例の WFA+-CSF1R、WFA+-M2BP、AFP、高感度 AFP-L3%、DCP、FIB-4 index、APRI を測定し発癌予測の AUC は有用性についいって検討した。

(1) WFA+-CSF1R は発癌群で 3 年前から高値を示していた。一方、WFA+-M2BP も発癌群で 3 年前から高値を示していたが WFA+-CSF1R ほど顕著ではなかった。

(2) WFA+-CSF1R は発癌前 3 年前の ROC 曲線の AUC で 0.7250 (0.6246-0.8069) と最も高値を示し次いで AFP、FIB-4 index、WFA+-M2BP で、WFA+-CSF1R は高発癌状態の一つの指標となる可能性が示された。

E. 健康危険情報

特記すべきことなし。

F. 研究発表

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G. 知的所有権の取得状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

Ⅲ.研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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